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PORADENOLYMPHITIS

Inguinal Poradenitis: Lymphogranulomatosis: Climatic Bubo, Etc.

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In the corresponding number of this *Bulletin* for last year (Vol. 30, pp. 423–29) the present writer,[1] under the title "Recent views upon Climatic Bubo and some allied conditions," drew attention to the very interesting results which had attended the co-ordination of clinical and laboratory observations upon a series of conditions whose pathogeny up to that time had baffled the clinician. It had been demonstrated that Climatic Bubo and Lymphogranuloma Inguinale were one and the same disease and that together with the conditions known as Chronic Elephantiasis and Ulceration of the Vulva, Esthiomène, the Genito-anorectal Syndrome and Inflammatory Stricture of the Rectum, were due to an infection with a specific ultramicroscopic virus which could be transmitted to and passaged in laboratory animals. A method of diagnosis by means of an intradermal antigenic reaction had been introduced by Frei and proved of the greatest value.

Shortly after that summary appeared, a monograph[2] was published giving a complete account of the history of the recognition of the several conditions, with a critical digest of all the published work on the subject, dealing with geographical distribution, aetiology, symptomatology, pathogenesis and pathology and a complete bibliography of over 900 references.

The present article therefore will be limited to a summary of such observations as have been published since the appearance of that monograph. General surveys of some part of the same ground have been published by several writers, among them Ravaut & Cachera,[3] Ravaut,[4] Hellerström.[5]

Nomenclature.

In the chapter[2] devoted to this question, attention was drawn to the multiplicity of terms which had been introduced and to the objections

which could be lodged against most of them. When the phrase "A Sixth Venereal Disease" was used it was specifically pointed out that it was employed with no suggestion that it should come into common usage. FAVRE,[6] to whom we owe the term lymphogranuloma inguinale, has recently cast it aside in favour of that proposed by FEISSINGER, viz., Poradenitis. This name, while covering all the conditions in which an adenopathy plays the chief part in the morbid process, is still open to criticism in that it is inapplicable to those conditions in which the glands are not involved and to the disease as produced in animals by intracerebral inoculation, conditions in which lymphatic tissues and spaces are infected. The term poradenolymphitis was put forward as an alternative but in turn does not quite meet the case, though it would appear to overcome some of the difficulties. When the glands are involved, as of course they are in the majority of infections, the fully expanded form por-adeno-lymphitis or poro-lymphadenitis might be used; in cases in which the glands are not involved the contracted form poro-lymphitis might be adopted. We could speak, as I have previously pointed out, of a peri-rectal por-adeno-lymphitis, of a por-adeno-lymphitic perimetritis, of a poro-lymphitic infection of the skin, of a poro-lymphitic meningo-encephalitis in the monkey: Climatic bubo might become poro-lymphadenitis inguinalis tropica, etc.

The objection that can be raised against the word lymphitis is that it suggests an inflammatory reaction in the lymph rather than in the walls of the lymph channel. Lymphatitis defined by Dorland as "inflammation of some part of the lymphatic system" might meet the difficulty in the form porolymphatitis. Lymphopathia venerea is another suggestion, but the term loses the specific prefix and is not so easily converted into derivative forms.

It would be a great advantage if this question of nomenclature could be settled by international agreement.

Geographical Distribution and Local Incidence.

In the last summary mention was made of the first case of an indigenous infection in this country with experimental proof of the nature of the condition[7] and of three cases subsequently recognized by ANWYL-DAVIES[8] at the Whitechapel V.D. clinic, all cases of inguinal poradenitis. Since then no other cases have been recorded in Great Britain. The infection may be rare but the author believes that if sought for, they may be recognized: all such cases should be recorded. SCHULMANN[9] thinks that the number of cases of I.P. (inguinal poradenitis) in Paris is on the increase: he had seen twenty-six cases in six months. LEVENSON[10] alludes to ten cases of the genito-ano-rectal syndrome in Moscow; WEIN, KERZENBERG & SILBERG[11] to three cases of I.P. in the same city. KALZ & SAGHER[12, 13] mention thirty patients suffering from I.P. treated in Prague. JONESCO-MIHAIESTI[14] and his co-workers draw attention to the spread of the disease in Rumania; LONGHIN[14] had seen ten cases in two years in the Bucharest Military Hospital. VERESS[15] speaks of the increasing number of cases being recognized in Transylvania. PERKEL & SOURGIK[16] state that the disease occurs over the whole Black Sea coastal area. From Italy there are numerous reports of cases of I.P. and of the genito-ano-rectal syndrome including those by CORACHAN[17] and by VERCELLINO[18] of Turin, DEL VIVO[19] of Genoa, LEIDI[20] of Brescia, SANNICANDRO[21] and JAJA[22], both of Puglia, MAZZANTI[23] of Florence.

Del Vivo has described four cases of the genito-ano-rectal syndrome in prostitutes with positive Frei reactions. Vercellino's patients were all suffering from I.P. Bizzozero had under his care in Turin in the twelve months 1932–33 fifteen males and eleven females suffering from the infection. He saw one conjugal case, two cases of ano-rectal disease and two of esthiomène, one of which gave a positive Frei reaction. Corachan writing upon inflammatory stricture of the rectum, upholds the virus of poradenitis as the causative agent. Sannicandro had met with twenty-three cases of poradenitic infection in Puglia; two had contracted their disease in Milan, the remainder at Bari. Cases of vulval ulceration and elephantiasis, ano-rectal disease and stricture are also cited by this author and by Jaja. De Gregorio & Murúa[24] give some interesting figures for Zaragoza, where among others they had come across nineteen cases of rectal stricture: all yielded positive Frei reactions. Bejerano & Gallego Calatayud[25] report having noted a great increase in the number of cases of I.P. in the summer of 1932 in Barcelona. A positive Frei reaction was found in 15 per cent. of forty-five prostitutes tested though none presented obvious manifestations of the disease. Later seventy-five prostitutes, stated to be without signs of infection, were submitted to intradermal antigenic inoculation: of these forty-nine returned and among these 11 per cent. showed positive results. They were all drawn from the lowest grades; others of higher station were all negative. This tallies with the findings of other observers; the disease is commoner among prostitutes of more degraded type. Barriola & Mañeru[26] refer to the same subject in San Sebastian.

In the United States the disease in all its forms has been discovered, chiefly in the coloured population, in such numbers that it can no longer be considered rare. This refers to indigenous infections and not to such cases as Wilmoth mentioned in 1928 when he stated that L.I. was met with relatively frequently in the coastal cities of the States, as nearly all these cases had contracted their disease elsewhere. A number of fresh cases have been published in the United States by de Wolf[27] of Cleveland, Ohio, and others. Wien & Perlstein[28] met with twelve male and four female Frei positive cases in eighteen months in Chicago. Martin's[29] figures in regard to stricture of the rectum in Philadelphia are interesting. A total of one hundred and sixty-seven cases had been seen; of these 81 per cent. were negroes, and all these were women, a fact which could not then be explained. More recently recourse was had to Frei's test, and twenty out of twenty-five gave positive results. It is interesting to compare these findings with those of Witherspoon[30] in New Orleans, to be mentioned later.

Ives & Katz[31] in describing a clinical case of L.I. in St. Louis refer to it as the first to be recognized west of the Mississippi. Tomlinson & Cameron[32] in recording three cases of L.I. with positive skin tests, coming under their care in Omaha believe them to be the first cases to be diagnosed west of Cleveland, Ohio. The disease—L.I.—as met with in Chile, is the subject of papers by Coutts[33] and by Coutts & Bianchi[34]; their observations will be dealt with under aetiology.

There are but few new observations from Africa; they include those by Moutot[35] (Morocco), Cohen[36] (Algeria), Advier & Riou[37] (Dakar) and Graham[38] (Tanganyika).

Graham has described three examples of genito-ano-rectal disease in women at Mwanza In the first the distribution was ano-rectal, in the second the vulva was affected and there was a vaginal stricture, in the

third condyloma-like masses were present about the anus and vulva, associated with ulceration in the lower third of the vagina and a recto-vaginal fistula. All had enlarged inguinal glands; in one suppuration had occurred. All had had syphilis but antisyphilitic remedies failed to improve their condition. These cases would seem almost certainly to be cases of porolymphitic virus infection. A history of syphilis is of course quite common because a large percentage of low-caste prostitutes have had that disease, but there is no evidence that it is a factor in the production of the condition. I would again like to draw the attention of all medical men practising among native races to the interest of this disease, and suggest the desirability of placing their observations on record, especially if supported by the results of skin tests. Clement CHESTERMAN[39] since his return to the Belgian Congo, has kept a watch for cases, and in a private communication tells me that he has already seen quite a number of examples of inguinal poradenitis, including one partner-case and also cases of the genito-ano-rectal syndrome. What would appear to have been a typical case of I.P. has also been reported to me by P. L. C. GARNHAM[40] from Voi, Kenya—a male native with large masses of glands in each groin and numerous discharging fistulae. One of the excised glands examined in England (G. Marshall FINDLAY) shows the typical histological appearances of poradenitis.

ADVIER & RIOU[37] have noted a number of cases of L.I. infection at Dakar. Their figures are—7 Europeans, 48 natives : 39 male, 9 female : 47 cases inguinal poradenitis, including 1 partner-case and 1 case of abacterial urethritis : all Frei positive but mixed infections not uncommon. Positive skin tests were also observed in (*a*) a prostitute with syphilis, but no signs of disease ; (*b*) five women with periproctitis and nodular perianal condylomata-like growths, of whom two also had rectal stricture and one vulval elephantiasis ; (*c*) a syphilitic man with thickening of the wall of the rectum and rectal fistulae ; (*d*) a European who had had an inguinal adenitis some years before.

In discussing the subject recently, Dr. A. P. DAVIES[41] informed me that these same conditions are to be seen among the native inhabitants of the northern half of the coastal zone of Western Australia. Dr. H. R. WORTH[42] vouches for similar observations in regard to southern China. PENNANÉAC'H[43] mentions the disease in Hankow. NGUYEN VAN TUNG[44] has seen one hundred cases of L.I. in Saigon.

Inguinal poradenitis is common in the Dutch East Indies ; BRANDON[45] came across one hundred and forty-five cases in 1931. This is confirmed by BONNE[46] and his colleagues.

Reference must also be made to the article by HELLERSTRÖM & WASSÉN[47] of Stockholm, who in 1932 issued a questionary to some 350 foreign dermato-venereological clinics and to medical men in Sweden concerning the incidence of L.I. infections. The analysis of the results of this investigation was presented in August 1933 and covers 1,636 cases of L.I. and 215 cases of esthiomène (genito-ano-rectal syndrome). It is not possible to summarise their findings here but it may be noted how not very uncommon the affection is in those cities in which investigations have been carried out.

The only other paper on " endemic climatic bubo " is by JANZ.[48]

Aetiology : Diagnosis : Frei's Intra-dermo-reaction.

The virus aetiology of L.I. and C.B. (inguinal poradenitis) is now established upon an unassailable basis. The possibility of co-existing

infections must never be lost sight of, as the clinical picture may be thereby obscured. That infection is contracted venereally is the rule though as has been before pointed out exceptions may occur, a point worthy of remembrance in the case of children. LOCKWOOD and HEIDT[49] in the discussion upon BRANDON's paper on L.I. in the Dutch East Indies, did not think the venereal origin of the disease was proved, the latter because he had seen the affection in an old impotent Chinaman. Such an observation proves nothing except perhaps that the man was old and impotent. In BRANDON's one hundred and forty-five cases of I.P., the intra-cutaneous test was positive in all. Extragenital primary lesions will be dealt with in a later section.

The aetiological relationship of the virus to those other conditions which have been considered as manifestations of the sixth venereal disease has been more difficult to prove and has in fact not yet found acceptance in all quarters despite the ever increasing amount of evidence in its favour. The importance of Frei's skin reaction as a means of diagnosis is of the greatest importance and its more extended use and better understanding are imperative.

There is a useful paper by SCHUMACHER[50] on the subject. Some observers have questioned the specificity of the test in some one or other direction, both in regard to cases of I.P. and cases of the genito-ano-rectal syndrome. It has been held that because some cases of I.P. do not react, therefore the test loses part of its value. It is true failure to react may occur, the development of skin allergy may be delayed, obscured or may fail under certain conditions as in the allergic reactions of other affections. Some of these conditions are known and so soon as they are better understood so will the test have an even greater value than at the present time. That it must be carried out with care and with certain precautions has been maintained by FREI from the beginning. Some cases may react with one antigen and not with another, suggesting the possible existence of different strains of virus, but this has not been proved. A specific reaction may be obtained by intravenous injection of antigen, and this sometimes when the skin has failed to react, as pointed out by GAY PRIETO.[51] Temporary desensitization of the skin may follow intra-dermal injections as shown by WIEN & PERLSTEIN.[28] Intra-dermal injections of antigen in 1/10 cc. doses at 3 to 5-day intervals using the skin of one forearm, results after eleven inoculations in loss of local reactivity, while the skin of some other part of the body, the back or the buttock, retains the power to react.

JERSILD[52] has again reviewed his cases of the genito-ano-rectal syndrome. He classifies them as follows :—(*a*) 5 cases of "syphiloma" with rectal infiltration and stricture at 4 to 5 cm. above the anus, perianal infiltration and fistulae but no genital changes, (*b*) 6 cases exhibiting the complete syndrome, elephantiasis vulvae combined with ano-rectal lesions, (*c*) 1 case of elephantiasis vulvae, affecting the left labia and clitoris with retention of urine and a stricture of the vagina 6 cm. above the vulva. All had negative W.R., but 8 of the 12 cases were syphilitics—in 4 the syphilitic infection preceded the other condition, in 4 it followed some 3–10 years later. Four denied syphilis and clinical and serological evidence was negative. In 66 per cent. of cases therefore syphilis could be excluded. In three the gonococcal fixation test was done with two negatives and one doubtful result. In ten gonococci were sought with negative result. The Ito-Riensterna reaction for chancroid infection was performed in eleven

cases, eight were negative, one doubtful, two positive. In one of the positives there was a history of chancroid. Frei's test was positive in eleven out of the twelve cases; in the twelfth case the reaction was doubtful with one L.I. antigen and negative with a second antigen, but it is interesting to note that in this case there was a history of an inguinal bubo as long ago as 1908, and that pus obtained from a fistula leading to a perirectal abscess yielded an antigen which gave positive results when skin tested in a number of L.I. patients, and negative results with controls. Three husbands were tested; all had had inguinal buboes; all gave positive reactions; all were negative to tests with Dmelcos. JERSILD believes that though most cases of the G.A.R syndrome are due to an L.I. virus infection, some proportion, however small, may not be so. He seems to think also that the elephantiasis is due to some secondary infection rather than due to the specific L.I. virus, and that the pathological changes are not specific. This is an attitude of extreme caution, and perhaps hardly warranted if all the accumulated evidence of others be considered.

An analysis of 48 unselected cases by BENSAUDE & LAMBLING[53] under whose care they came for ano-rectal disease is worthy of study. Of the 48, 27 with inflammatory stricture of the rectum were submitted to Frei's test—in 24 the reaction was positive; among these there had been a suppurative inguinal adenitis in 9, 3 exhibited the complete G.A.R. syndrome and 3 showed perianal growths. Further they found that among 10 cases suffering from an apparently simple rectitis or ano-rectitis, 4 yielded positive reactions and 3 partially positive reactions. In 11 patients there were abscesses, or fistulae resulting therefrom, at the anal margin. While these authors believe that the majority of cases of inflammatory stricture are due to the porolymphitic virus they are not prepared to say that there may not be a few cases of gonorrhoeal, syphilitic or tuberculous origin. They have argued that because in one of their most typical cases of rectal stricture, with ulceration, fistula-formation and inguinal bubo, the Frei reaction was negative, therefore the case was due to some other cause than the L.I. virus. This argument is, I think, not sound. It should first be established that the virus is not the cause by using other available methods of investigation and be proved what other cause is effective.

Other co-existing venereal infections have by some been considered as factors in the production of G.A.R. disease; such a coincidence to my mind should only be looked upon as indicating the greater chance of venereal infection of all kinds. This is well shown by some figures given by BENSAUDE[54] and reproduced by LOUSTE & MÉZARD.[55] Between 1910 and 1930 (before the introduction of Frei's test) 289 cases of rectal stricture were seen; of these, data are available in 226, among whom 186 were classed as inflammatory strictures. In only 12 of the 186 was there no history of venereal disease. 139 had had syphilis but there was no evidence that that disease was a causative factor. The following figures are given:—syphilis alone 84; syphilis and sodomy 50; syphilis and gonorrhoea 11; syphilis and chancroid 3; syphilis and tuberculosis 3; gonorrhoea alone 8; gonorrhoea and sodomy 4; sodomy alone; sodomy and chancroid 2.

BELGODÈRE[56] sees in an L.I. virus aetiology a complete explanation of all the facts concerning inflammatory stricture of the rectum and the so-called syphiloma ano-rectal of FOURNIER, but he in his turn has described at great length a case under his own observation since 1912 which he believes to be syphilitic in origin without apparently taking

the ordinary means by Frei's test of excluding a virus pathogeny. There is in fact nothing to support his thesis save his opinion.

SANTY[57] has similarly described a case in Lyon as one of syphilitic stricture of the rectum which clinically would appear to be one typical of virus infection, and he in the same way has adduced no evidence in proof one way or the other.

GOUGEROT & CARTEAUD[58] are among those who believe that cases of "recto-ano-genital elephantiasis may have a varied pathogeny and would include streptococcal infections, mycosis, tuberculosis, etc.," among the possible causes, basing their beliefs not so much on positive evidence in regard to these other supposed causes as on the negative Frei reactions in some proportion of cases, a position open to fallacy I think.

Reference has been made to the case of esthiomène associated with rectal stricture described by STEIN & HEIMANN of New York (1912) in which they postulated gonorrhoea as the cause and to STEIN's paper on syphiloma vulvae (1920), when he was inclined to believe that all these conditions were syphilitic in origin. In 1925 that author[59] published another case of syphiloma vulvae and again upheld the syphilitic origin of the condition. At that time, of course, porolymphitic infections as the possible cause were unknown and Frei's test had not been introduced. In 1933, however, in a paper on diseases of the vulva, STEIN[60] still apparently believes in a syphilitic pathogeny for cases which would appear to be perfect examples of the G.A.R. syndrome, but poradenitis is not even mentioned, no skin tests were done and no attempt made to isolate the virus. In the absence of such investigations the cases have no value.

Typical cases of the vulval affection with inguinal poradenitis and positive skin tests have been recorded by LÉPINAY & GRÉVIN[61] at Casa Blanca. RICHTER[62] has published a case of esthiomène with vaginal stricture and positive skin test in Berlin. OBRTEL[63] has also dwelt on the relationship between L.I. and chronic ulceration of the vulva. The Italian cases have been mentioned above. There is a note upon lymphogranulomatosis by LANGER.[64] COLE[65] of Cleveland, Ohio, has brought his figures up to date. He has observations upon 36 male and 1 female case of I.P. : 22 of these cases were negroes, 15 whites ; in 21 the affection was unilateral, in 13 bilateral ; 18 showed a primary lesion, 3 had a urethritis ; in 3 conjunctivitis was noted, in 3 arthritis was present, in 2 erythema nodosum or multiforme. All yielded positive reactions to Frei's intradermal test. At the same time 1 white male, 1 coloured male, 2 white females and 11 coloured females came under observation with genito-ano-rectal disease. Six of these had positive W.R. but all fifteen gave positive Frei reactions. Among these cases were two of esthiomène type, of whom one had a rectal stricture as well, and one male with elephantiasis scroti and rectal stricture. All the others exhibited stricture of the rectum with indurated cauliflower-like perianal lesions. WITHERSPOON'S[30] twenty-six cases of vulval elephantiasis collected during the twenty years ending 1932 may also be mentioned. They were all coloured women under observation at the Charity Hospital, New Orleans. In 9 the W.R. was not done. Of 17, it was negative in 9 and positive in 8. These cases were all considered to be examples of syphilitic elephantiasis of the vulva, but it should be remarked that no mention is even made of poradenitic virus infections and no tests were carried out.

COUTTS & BIANCHI[34] of Santiago, writing on their observations upon inguinal adenitis in Chile, state: "the more extended use of the intracutaneous reaction of Frei has proved that this biologic test is not always specific." Before such a statement can be accepted, the grounds upon which it is based will need careful examination. These authors believe that errors occur "due to the fact that among the different symptoms ascribed to Nicolas and Favre's disease there exist two different diseases which give a positive reaction only when the proper antigen is used as a test." I think it will be apparent from what is stated by the authors that the errors are entirely of their own making and that Frei's test comes out triumphant.

They postulate virus A. "which determines the following conditions preceded by the appearance of an ulceration on or around the genital organs or anus—inflammation of the inguinal lymph nodes (poradenitis of N. et F.), esthiomène vulvae, elephantiasis penis et scroti (BARTHELS & BIBERSTEIN) and chronic stricture of the rectum (JERSILD, FREI & KOPPEL)"; and virus B., which determines the appearance of systemic symptoms resembling those that precede the initiation of most infectious diseases; "after a few days the inguinal, deep iliac, mesenteric, lumbo-aortic and other lymph nodes appear inflamed"; an exanthem and arthritis may occur; "no apparent site of inoculation can be found on or around the genital organs." "These different viruses are of buccal origin . . . cunnilinguism and other abnormal practices." Affections due to virus A. (36 cases) give positive skin reactions with an A. antigen and are negative to B. antigen and conversely with those cases due to B. virus (18 cases). For the first group COUTTS has used the term "sporadic disease of NICOLAS-FAVRE," to the second group he most unfortunately refers as "epidemic climatic bubo." The first group are obviously cases of poradenolymphitis. The second infection which occurs in epidemic form in the spring and counts among its other symptoms enlargement of the liver and spleen, and an eosinophilia, which it is stated may reach 20 per cent., is equally obviously nothing to do whatever with climatic bubo or poradenitis. The disease resembles more the epidemic adenitis described in Italy some years ago (SEMERO 1929, ISOTTI 1930, *et alia*) and is very suggestive of Tularaemia. These Chilian cases have been discussed at some length as the dicta expressed by COUTTS needed contradiction.

Positive skin reactions with poradenitic antigens have been found in persons who at the time have presented no obvious signs of infection. The observations of BÉJARANO and GALLEGO CALATAYUD[25] have already been referred to. Clément SIMON[66] similarly found that 10 per cent. of a series of prostitutes gave positive reactions. SÉZARY & LÉNÈGRE[67] and others have made similar observations, and the question of "carriers" has been raised. Carriers may or may not occur but it would be a wise man who could state with a certainty that in such cases no minimal lesions were present in the complicated system of the genito-urinary and lower intestinal tracts.

SCHULMANN[9] obtained positive Frei reactions in the mistresses of two men suffering from L.I., who "only had a mild metritis." There was nothing to show, however, that the metritis was not of virus origin.

LÉPINAY & GRÉVIN[61] performed cutaneous tests on 79 women at Casa Blanca using a monkey-brain antigen. In only 1 was a positive reaction obtained, a woman suffering from a chronic vulval ulceration, proved not to be due to syphilis, chancroid or tuberculosis. Another

woman, not in this series, who had typical vulval elephantiasis yielded a positive skin test ; both, it is interesting to note, had had a suppurative inguinal adenopathy. Eleven males and one female exhibiting typical I.P. all gave positive Frei reactions.

LANZENBERG[68] has recorded a case "simulating" inguinal poradenitis with primary lesion in which W.R., Dmelcos test and gland puncture were all negative, dark-ground examination negative, and Frei reaction negative. A smear from the urethra was positive for gonococci. No softening of the glands occurred and the condition cleared up. This case certainly suggests a "forme fruste" of I.P., associated with gonorrhoea in which the virus infection did not proceed far enough to excite skin allergy. It would have been interesting to have seen the result of intra-cerebral animal inoculation of gland pulp.

Symptomatology : Differential Diagnosis.

Much has already been said on this side of the subject but attention will here be drawn to some further points which have been brought forward in recent papers.

The primary lesion, as is well known, may be very small and evanescent ; on the other hand it may reach considerable size and form a nodule ; in some cases it may present an appearance resembling a syphilitic chancre, as was originally noted by BORY and later by SÉZARY & PERRAULT.[69] SÉZARY & LÉNÈGRE[70] at the same time have drawn attention to chancroid-like initial sores. Mixed infections must never be forgotten. LÖHE[71] has described an excellent example of the primary lesion in the female, in his case situated at the orifice of Bartholin's duct. That the initial lesion may lie within the urethra is of course known. DE WOLF has published a good example—a coloured male with no visible penile lesion but a urethritis with bilateral inguinal bubo, Frei test positive, W.R. negative, gonococcus negative by urethral smear and gland puncture. He has recorded a similar case in a white man as have also LANZENBURG & ZORN.[72] Similar pictures have been observed in tropical cases—climatic bubo. Probably every case of abacterial urethritis should be investigated as a possible case of virus infection. The possible relationship of such cases to those known as urethritis of Waelsch type and venereal urethritis of unknown nature, recorded by HISSARD & HUSSON, is of interest.

COHEN[36] of Oran has reported somewhat analogous cases in men and their wives, and BEZECNY[73] treats of the same subject.

Records of extra-genital infections apart from those in the ano-rectal region due to sodomy remain few in number, but CURTH[74] of New York has added one well authenticated case to the list. A negro ten days after practising cunnilingus developed on the tip of the tongue some non-painful blister-like lesions with considerable local swelling, followed by a glandular enlargement in the neck, forming a huge mass. Dark-ground examination of the exudate from the sores on the tongue was negative for spirochaetes. W.R. negative, no evidence of tuberculosis nor of a mycotic or Ducrey infection, Frei reaction positive ; an antigen prepared from the gland pus yielded positive reactions in L.I. patients and cases of ano-rectal disease and of rectal stricture. An almost exactly similar case has been recorded by BLOOM.[75]

In 1932 LÉPINAY & GRÉVIN described a case of L.I. in which they suggested that infection had gained entry through a wound on the foot. In referring to this case at the time I considered that the evidence did

not warrant such a belief. This opinion has since been supported by GATÉ[76] so that once again it may be said that no such case of peripheral infection is known. FRANCHI[77] of Turin has shown that the skin involved in an inguinal poradenitis contains the virus in many cases by demonstrating that skin blister fluid gives a positive skin reaction in L.I. patients.

Reference has been made to meningeal symptoms in human poradenitic infections. This led MIDANA & VERCELLINO[78] of Turin to investigate the cerebrospinal fluid from eleven cases of typical I.P. with positive Frei reactions in which syphilis was excluded. In nine the C.S.F. was normal. In one the reactions of Pandy, Nonne, Weichbrodt and of Boltz were positive; in another these reactions were all positive with the exception of the Pandy reaction The protein content was increased—30 cgm. and the cell elements were above normal, in the first case reaching 46. The amylolytic activity was low in all eleven but absent in the two cases detailed above. The C.S.F. from these two cases gave positive skin reactions in L.I. patients, the others were negative. A case of some interest is reported by LAFARGUE and colleagues[79]. All other treatments having failed in the hands of some other medical man, they cleared out the whole of Scarpa's triangle by curettage. Eight days later the patient developed general anasarca and polyuria with 9 gm. of albumin per litre. There was an aseptic pyuria and no blood urea retention. After eight weeks improvement began and health was restored in seven months. The authors wonder whether this was a nephropathy due to the virus of L.I.

Elephantiasis following upon the surgical extirpation of poradenitic inguinal glands and subsequent "erysipelatous" attack is well exemplified by a case detailed by LOUSTE, CAILLIAU & SCHWARTZ.[80]

Several authors have given descriptions of the evolution of the conditions included under the term genito-ano-rectal syndrome. It will be remembered that these conditions were generally considered to be due to a redux specific virus cellulitus along lymphatic channels running to affected glands. That this certainly is not always the case must not be lost sight of since it is known the skin and subcutaneous tissue alone may be affected. The following observations by GOUGEROT & CARTEAUD[58] are given at some length therefore as they possess a particular interest.

Early cases of the syndrome are seldom seen and it is only rarely that it is possible to follow its evolution. In the three cases now described the earliest lesion was a localized hypertrophy of a single fold of skin about the anus, or a limited sector of the vulva. In all three there was a history of syphilis. In the first it seems clear syphilis played no part, the Frei reaction was positive, and no other factor was involved. In the other two the Frei reaction was not carried out, they were old syphilitics and it is open to anyone to suggest that syphilis was a factor. The early lesion commences as a nodule, softening occurs and an abscess forms which opens on the surface by a fistula. This nodule is referred to as "La gomme du N-F." About these nodules the elephantiasic process begins, it is said, without any involvement of glands.

Case 1. A thickening of an anal fold occurred 2½ years before coming under observation; this had enlarged and on examination six small follicular lesions were found on the left labium and adjacent parts of the buttock, their orifices exuding a small amount of mucopus; some small

glands were present in the groin. In one of the lesions spirochaetes were discovered, a finding which, taken with the fact that the W.R. was negative and the Kahn feebly positive, the authors believed to indicate an early secondary infection of the follicular lesion with syphilis. Treatment for syphilis was instituted and cure established by July 1932. A year later the anal fold had undergone much greater enlargement into a cock's-comb like structure (so characteristic of the condition) with a prolongation into the anus. There was swelling of the labium with a resemblance to a localized elephantiasis. On the buttock were a number of nodules some of which had undergone softening, and opened on the surface by fistulae; others were found between the vulva and anus.

Frei's test was positive: Tuberculin test positive: Dmelcos test negative: streptococcal skin test negative: staphyloccal skin test mildly positive: gonococcal culture negative.

Case 2 was that of a woman with a history of anal chancre in 1922. The anal lesion under discussion began in 1925 while under treatment for syphilis, and remained unaffected by the treatment. It resembled that in Case 1, and there was besides, an abscess on the buttock. In 1928 marked infiltration and elephantiasis of the anal region and buttock was manifest with multiple fistulae in ano and a rectal stricture. The case then passed out of observation and no Frei test was done.

In the third case there was a history of anal chancre in 1916 and gonorrhoea followed by hemiplegia and icterus. In 1922 pulmonary tuberculosis supervened. (The husband had died of phthisis, the father was suffering from phthisis and syphilis.) When seen in 1925 there was a condition about the anus as in the last case, a thickened right labium and a perineal nodule. Frei test not performed.

There is also an interesting Frei-positive case published by Gaté, Michel & Chapuis[81]—W.R. negative, Ducrey negative, treponema negative. Oedema of the labia majora and preputium clitoridis associated with herpetiform lesions about the vulva and some small glands in the groins was followed by the development of a papillomatous condition of the anorectal region and stricture of the rectum.

A case by Gougerot, Cohen & Patte[82] also deserves notice. Following upon a small suppurative lesion at the anal margin four years before, there developed an elephantoid condition of the skin of the inner sides of the buttocks with some twenty fistulous openings, swelling of the left labium to twice the normal size, with polypoidal overgrowth and a bilateral non-suppurative adenopathy. W.R. reaction uncertain, Dmelcos test negative, tuberculin test strongly positive but guineapig inoculation negative. The Frei reaction in this case was negative but an L.I. pathogeny should not perhaps be ruled out without further investigations having been made.

Differential Diagnosis.

Pautrier & Lanzenberg[83] have recorded an excellent example of the difficulties which may be encountered in the clinical diagnosis between poradenitis and an inguinal tuberculous adenitis.

Favre[6] has described two groups of cases which may and indeed did cause some difficulty in clinical diagnosis. The first group he designates "Bubons cancéreux d'aspect inflammatoire," illustrated by (1) a case from which an inguinal gland was submitted for examination, removed from a 58-year-old male under treatment for nervous syphilis. (2) The case of a 32-year-old woman recorded by Louste, Thibaut & Chavany in the first place as "un cas de lymphogranulomatose subaïgne evoluant chez une femme" (*Bull. Soc. franç. Dermat. et Syph.* 1923, p. 340) and later diagnosed as "epithelioma de la région inguino-vulvaire considéré comme une lymphogranulomatose" (*Ibid.* 1933, p. 404). (3) and (4) Two cases coming under his own observation.

The features common to all these cases which resembled those of L.I. consisted in the appearance of enlarged glands in the groins with slow evolution, later reddening of the skin, softening of the glands, abscess formation and fistulation, associated with enlargement of the iliac glands. Sections of glands removed in each case revealed them to be "epitheliomatous." No primary lesion was discovered in any case during life and in no case was an examination made after death.

In no case was Frei's reaction performed; it is of interest to speculate what might have been found.

The second group of cases FAVRE alludes to as "Cellulites torpides en nappe de l'aine"—three cases in which was found, in each, a flat, raised, well-defined, hard, indurated plaque involving the skin and subcutaneous tissue of the inguinal region, Scarpa's triangle and the adjacent area of the pubes.

The mass was not adherent to deeper structures, was unilateral in all three cases and there was no associated glandular enlargement. Pain was slight, the skin a lilac-rose colour, there was no bossing. Suppuration did not occur and after running a rather chronic course the condition cleared up. This lesion is not tuberculous nor mycotic in origin. Two of the patients had active syphilis, the third was suffering from general paralysis but antisyphilitic treatment had no effect on the condition, which is therefore said to be of unknown pathogeny. Again it would have been interesting to have Frei-tested these cases. Pathologically the lesions showed a sclerosing inflammatory reaction, the predominating cells being fibroblasts, lymphocytes and connective tissue cells like histiocytes, a few polymorphs and rarely a plasmocyte. Deposits of cholesterin and blood pigment were noted and an obliterative thickening of blood vessels was revealed but no micro-gummatous changes with epithelioid abscesses as in L.I.

ADVIER & RIOU[84] in Dakar have drawn attention to the real difficulty that may exist in attempting the differential diagnosis between poradenitis and plague. They had seen eight cases of P.I. in which the initial diagnosis had been plague and conversely four cases of plague which had been taken as P.I.

Treatment.

There is very little new to chronicle. DE WOLF mentions a good result after a total of 38 cc. of one per cent. tartar emetic solution intravenously. LEIDI[20] speaks of the excellent effect of neostibosan. BRANDON[45] found injections of milk, X-rays and solux more useful than antimony or gold preparations. DE ALMEIDA TOLEDO[85] of San Paulo uses fouadin. PERKEL & SOURGIK[16] have tried injecting 1·5 to 2·0 cc. glycerin into the affected glands, also 0·4 to 1·0 cc. milk into the glands after aspiration of pus with 2·0 to 3·0 cc. follow-up doses at intervals of 2 or 3 days. X-ray therapy is dealt with by MCALPIN & GOLDEN[88]. CHEVALLIER & FIEHRER[86] call attention to the good results which may be obtained with sodium salicylate in non-fistulated cases: 6 to 8 gm. are given each day by mouth, the patient being kept on a milk diet, or ½ to 1 gm. in glucose solution is given intravenously when a normal diet may be enjoyed. TOURAINE & AUBRUN[87] also in a few similar cases obtained excellent results with this drug, giving 6 gm. by mouth daily and at the same time 1 gm. intravenously for 30 days. WIEN & PERLSTEIN[28] have tried 1/10 cc. antigen intradermally at 3 to 5 day intervals in 12 male and 4 female Frei positive cases with improvement. In a single male case of ano-rectal

disease improvement was also seen. GAY PRIETO[51] considers intravenous antigen therapy the method of election. Considerable reactions may be produced but these decrease in severity as desensitization occurs. He thinks this form of treatment should be tried out in rectal cases as well as in poradenitis. KALZ & SAGHER[12] praise the good effects following treatment with convalescent serum in 30 Frei positive cases of L.I. The treatment may take 4 to 6 weeks ; 5 to 10 cc. are administered intramuscularly at 3 or 4 days interval to a total of 60 to 150 cc. : normal serum is without effect.

Experimental Investigations.

LÖHE, ROSENFELD, SCHLOSSBERGER & KRUMEICH[89] have succeeded in transmitting the virus from the primary lesion to monkeys on two occasions, in the first from a primary sore on the penis of a man, in the second case from a similar lesion situated at the opening of Bartholin's duct in a woman. From the monkeys passage to guineapigs was effected and from them back to monkeys. Antigens prepared from the monkeys' brains and the guineapigs' groin glands gave positive skin reactions in L.I. patients. COHN & KLEEBERG[90] have now demonstrated that an antigen prepared from the meninges of a monkey killed on the sixth day after an intraperitoneal injection of 4·0 cc. L.I. pus, though the animal show no sign or symptom of peritoneal infection, will give a mild skin reaction in L.I. patients, comparable to that evoked by an antigen prepared from the omentum, controls all being negative.

WASSEN[91] has confirmed the infectivity of white mice so well illustrated previously by Marshall FINDLAY. So excellent an experimental animal is the mouse that in regard to porolymphitis one might speak of "cultivating the virus *in vivo*." The virus after seven passages in mice was virulent for man, skin allergy developing on the eighth day after inoculation. LEVADITI and his colleagues[92] have also confirmed the ease with which the virus may be transmitted in mice by brain to brain passage and that after mouse passage the virus remains infective for monkeys. After many passages in mice a fatal systematized infection may be produced. LEVADITI & REINIÉ[93] in single experiments injected 5 cc. of a virulent brain emulsion into the spleen of one monkey and into the wall of the intestine in a second animal. Each was killed on the forty-first day. In the first animal the spleen and liver were demonstrated to contain the virus by injecting emulsions of these organs into the brains of mice. The brain, axillary glands, kidney, muscle, marrow, blood and lung were negative when so tested. In the case of the second animal a localized, thickened, congested lesion resulted with induration and hypertrophy of Peyer's patches. There were typical lesions in the mesenteric glands and changes in the spleen. The virus was also shown to be present in the axillary glands, kidney and bone marrow by mouse inoculation. BONNE[46] and his co-workers have also done some confirmatory work on animal transmission using the virus of "climatic bubo" in the Dutch East Indies. They note that an antigen prepared from monkey brain heated to 60°C. on two consecutive days injected into three volunteers, produced in them after 1½ to 6 weeks a typical axillary poradenitis and argue that the virus is not killed by this temperature. All other observers have found this method of preparation effective which rather suggests that the technique used in the D.E.I. was faulty ; at all events the observation needs confirmation.

There are two papers by JONESCO-MIHAIESTI[94, 95] and his colleagues following up previous work. Intra-peritoneal inoculation of monkeys with either pus or gland emulsions from 20 Frei-positive cases of L.I. demonstrated that there was some variability in virulence but in all a specific characteristic peritonitis was produced. The virus was present in the exudate and in the mesenteric glands and emulsions of these gave positive Frei reactions. Positive reactions were also obtained with antigens prepared from the brain and cord. The inoculation in the monkey may result in a septicaemia with haemorrhages in viscera and in the thyroid and adrenals associated with the acute peritonitis, or a subacute infection may occur which causes death in 30 to 40 days, with production of a subacute hyperplastic peritonitis and the formation of miliary granulomata, an adhesive pleuro-pericarditis and signs of paralysis in the hind limbs. In a third group of cases there is a progressive cachexia with anaemia, wasting and nervous symptoms, and at necropsy there is found marked thickening of the visceral peritoneum of the spleen and liver with adhesions, and hypertrophy of the abdominal lymphatic system. In yet another group after 10 to 15 days with signs of a mild peritonitis everything clears up. In another series of experiments these workers have confirmed the variability in susceptibility of monkeys. They have also found that in monkeys inoculated intraperitoneally there may develop an acute neuritis of the posterior nerve roots with demyelinization of the nerve fibres and an ascending degeneration in the posterior columns of the cord as in tabes while the inflammatory reaction is similar in cell picture to that seen in the reaction to L.I. virus elsewhere, and goes on to the formation of micro-granulomata.

Histopathology.

There are references to the pathological changes in poradenitic infections by FROBOESE,[96] VERCELLINO,[18] BONNE & his colleagues,[46] Franz KOCH,[97] but they do not call for special notice.

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MALARIA.

MER (G.). **Observations on the Development of *Plasmodium malariae* Lav. in *Anopheles elutus* Edw. Experimental Transmission of Quartan Malaria to Man from the Mosquito.**—*Ann. Trop. Med. & Parasit.* 1933. Dec. 20. Vol. 27. No. 4. pp. 483–488.

Three volunteers were infected by the bites of *A. elutus* which had been infected with *P. malariae* experimentally.

These experiments were carried out in the Huleh area, Palestine, where quartan malaria predominates throughout the whole year. Mixed infections with *P. falciparum* are very common. The development of *P. malariae* in the mosquito is relatively slow. Ripe *P. malariae* oocysts, up to 80μ in diameter, were not found until after 28 days. Ripe *P. vivax* cysts, 40μ diameter, were found after 17 days or earlier; and *P. falciparum* cysts, 54μ, after 18 days or earlier. The sporozoites of *P. malariae* were larger and more active than those of the other species. Three volunteers were infected with quartan malaria by the bites of *A. elutus* which had been experimentally infected by feeding on patients. Although large numbers of *A. elutus* were fed on patients whose blood contained gametocytes which exflagellated readily, it appears that few became infected. *W. Fletcher.*

GIOVANNOLA (Arnaldo). Caratteristiche alterazioni delle glandole salivari dell' *Anopheles maculipennis* infetto da parassiti malarigeni. (**Characteristic Changes in the Salivary Glands of "Anopheles maculipennis" infected by Malarial Parasites.**)—*Riv. di Malariologia.* 1933. Nov.–Dec. Vol. 12. No. 6. pp. 1140–1146. With 12 figs. on 2 plates. English summary p. 1217.

The author gives in tables the measurements of the salivary glands of ten normal and ten infected specimens of *A. maculipennis*, the anterior and posterior parts of both lateral and the median lobes. The averages of length do not reveal much difference, but the averages of the maximal widths of the posterior parts of the lateral lobes and of the median lobe are very different. The following is made up from the tables produced :—

	Average maximum width in microns		
	1st lateral lobe	2nd lateral lobe	Median
Normal glands	91	75	83
Infected ,, ...	115	126	103

In colour the normal are pearly-grey and refractive to light, fairly firm and easily dissected ; the infected glands are brown, not refractile but opaque and very fragile.

These changes are sufficiently obvious under a magnification as low as 10 diameters to enable a diagnosis of malaria infection to be made without proceeding to dissection. *H. H. S.*

HENRY (X.). Seroflokkulation bei Malaria. Technik und Anwendung in der Praxis. [**Technique and Practical Application of Serofloccculation in Malaria.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1934. Mar. Vol. 38. No. 3. pp. 93–100.

The discoverer of this method of serodiagnosis gives a detailed description of his technique and its practical applications in the diagnosis of malaria.

The author elaborated his method after having considered for a long time the Wassermann reaction in syphilis. A sentence in the Handbook on Tropical Diseases by KELSCH and KIENER interested him greatly. It ran as follows :—" All histopathological lesions in malaria are occasioned by the deposit in the organs of two pigments, the brown iron-containing pigment and the black pigment, the so-called melanin pigment, whose composition is not fully understood." The author considered that these pigments were not merely deposits but were active. They were malarial endogens and either produced antiendogens or disturbed the colloidal state and produced certain flocculating peculiarities of the serum. The preparation of true malarial melanin presented great practical difficulties, so he investigated other substances with pigment like that of malaria ; the first was a substance containing iron, the second containing melanin.

He found the ferroflocculation reaction was not absolutely specific for malaria, but the melanoflocculation reaction was specific and also more sensitive. He then gives a very complete and detailed description of his method for carrying out the reaction, which should be read in original by all workers employing or proposing to employ his reaction.

As regards its particular applications, he considers it will be valuable in malignant tertian infections in which no parasites are to be found in the peripheral blood, either from their being lodged in the internal organs or having disappeared following administration of a specific drug. In the latter case the blood should not be taken, if possible, within 24 hours after administration of the drug. Also it will be useful for diagnosis in the intervals between attacks of fever, when the reaction is strongly positive ; it may be weak during the febrile paroxysm. In the slight and chronic cases of malaria also the reaction is strongly positive ; in these cases the parasite is very rarely found.

Another interesting problem was dealt with, namely, that of persons who have contracted malaria in the tropics and returned to temperate climates. Professor RIEUX of Paris considers that for practical purposes malaria is cured after 2 years' residence in a temperate climate. CHAUFFARD disagrees with this view. ZIEMANN in Germany considers that malaria persists rather longer than 2 years. Numerous serological examinations of persons who had contracted malaria during the war and in the colonies showed that only 1 to 1·5 per cent. gave positive reactions. So a chronic malarial state in these persons is the exception ; the exceptional cases can be investigated by the melanoflocculation test.

The author directs attention to a matter which he has dealt with before, viz., that the treatment of chronic malaria is greatly helped by administration of extracts of liver and spleen since they appear to activate the specific drugs, and thus a better result is obtained than when the latter are given alone. The flocculation test becomes

negative under this treatment. He hopes that his method will prove of value in the future in connexion with the diagnosis and treatment of malaria. *E. D. W. Greig.*

VOIGTLÄNDER (W.). Untersuchungen ueber die Serumflockungsreaktion bei Malaria von Henry. [**Henry's Serum Flocculation Reaction in Malaria.**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1934. Feb. 15. Vol. 81. No. 5/6. pp. 377–400. [18 refs.]

Observations carried out on Henry's flocculation reaction in cases of malarial infection of man and animals.

As antigen the author employed melanin derived from the choroid of the eye of the ox; he considers this more sensitive than iron. In his technique he employs a formalin control which excludes cases of kala azar by giving a positive formol-gel reaction in that disease. He employs only half the amount of serum, 0·1 cc., and reagents recommended by HENRY. The test is carried out in 5 tubes. The tubes are placed in a water bath at 37°C. for 2½ hours and then they stand at room temperature for half an hour. At the end of 3 hours the results are read. He divides his work into two parts. In the first he deals with the reaction in cases of inoculation malaria, normal human sera and in sera of patients without malaria. In the second part he records the results of his investigations on the reaction in different experimental animals, chronic piroplasmosis of dogs, bird malaria, and birds infected with halteridia. In all about 224 sera were investigated.

From his research he concludes:—In acute human malaria the reaction is positive. Patients who have suffered from other diseases but not malaria give a negative reaction. He has had only once a definitely positive reaction in another disease, namely, secondary syphilis. In acute, latent and chronic malarial infection of birds the reaction is positive also. In piroplasmosis of dogs and other animal infections (halteridia) related to malaria the reaction is negative. In inoculation malaria in general paralysis in men the reaction gives a fairly accurate picture of the development of the malaria and indicates the disappearance of the infection after treatment He considers that Henry's melanoflocculation test is of considerable value in the diagnosis of malaria, and fills a lacuna, which had hitherto existed in the recognition of malarial infection. *E. D. W. Greig.*

CHORINE (V.) & RODIEUX (M.). La réaction de Henry et le diagnostic du paludisme. [**Henry's Reaction in Malaria.**]—*Bull. Soc. Path. Exot.* 1933. Dec. 13. Vol. 26. No. 10. pp. 1249–1252.

The authors subscribe to the usefulness of Henry's reaction in the diagnosis of malaria.

Between November 1932 and November 1933, the authors employed Henry's reaction in 171 cases. The first group consisted of 87 men who had suffered from malaria in the great war, or who had lived in France for more than two years after residence in the colonies. Of these, 94 per cent. were negative, 2 per cent. were doubtful, 4 per cent. were positive. The second group consisted of 74 men without parasites in their blood who had returned from the colonies during the last two years. Of these, 72 per cent. were negative, 11 per cent. were doubtful, and 17 per cent. were positive. The third group consisted of men who had returned from the colonies within two years and who had parasites

in their blood. Seventeen of them were positive and 4 negative. Two of the negative cases were in the middle of an attack when the blood was taken. Positive reactions diminished with treatment, and disappeared in 30 to 60 days. *W. F.*

GERBINIS (P.). La réaction de Weil-Félix est négative dans le paludisme. [**(Henry's Reaction in Typhus and) the Weil-Felix Reaction in Malaria.**]—*Bull. Soc. Path. Exot.* 1934. Jan. 10. Vol. 27. No. 1. pp. 19–20.

Henry's reaction is positive in typhus, and follows the curve of the Weil-Felix reaction, but the Weil-Felix reaction is not positive in malaria [see this *Bulletin*, Vol. 30, p. 892]. *W. F.*

TAREJEW (E. M.) & POUTCHKOVA (A. I.). Sur l'exploration fonctionnelle du système réticulo-endothélial dans le paludisme. (**Investigation on the Function of the Reticulo-Endothelial System in Malaria.**)—*Riv. di Malariologia.* 1933. Sept.–Oct. Vol. 12. No. 5. pp. 859–872. [17 refs.] English summary (9 lines) p. 1063.

The Congo-red test did not demonstrate clearly a blocking of the R.E. system in malaria.

The importance of the reticulo-endothelial system in immunity is well established. Natural immunity is lowered by its blockage; for example, KRITCHEVSKY inoculated mice with a strain of Dutton's spirochaete which was non-pathogenic, but when the R.E. system was blocked with saccharated iron the infection killed 46 per cent.; or, if the spleen was removed at the same time, 90 per cent. Similar results have been obtained with monkeys infected with non-pathogenic malaria parasites (see KRISHNAN, SMITH & LAL, *ante*, p. 179). In human malaria there is a blockage of the R.E. system by melanin, and RUGE attributes the lack of complete immunity to this cause. In order to test the capacity of the R.E. system ADLER has employed intravenous injections of Congo-red, a nondiffusible substance which is removed from the blood by this system. The co-efficient of Congo-red is the percentage which remains in the blood, one hour after the inoculation of 10 cc. of a 1 per cent. solution. The authors found this to be between 65 and 66 in non-malarious subjects. They expected to find a high index in malaria owing to failure of the blocked R.E. system to take up the Congo-red; but they were disappointed for in acute and severe cases the index was approximately normal. In non-complicated malaria there was a tendency for the index to decline and for the monocytes to increase as the health of the patient improved, and it is suggested that this may be a manifestation of immunity. *W. F.*

LANDEIRO (Fausto). Die Blutsenkungsreaktion bei Malaria. [**Sedimentation Index in Malaria.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1934. Jan. Vol. 38. No. 1. pp. 38–41. With 2 figs.

A series of observations carried out in cases of malaria on the sedimentation of red cells of the blood.

144 patients were investigated of which 71 were men and 73 women. 55 were infected with *P. vivax*, 2 with *P. malariae*, 21 with *P. falciparum*, 3 with *P. vivax* and *falciparum*, 27 were doubtful, and 34 negative. As the result of his investigations the author reaches the

following conclusions :—The sedimentation index is increased in cases of malaria. The increase is more marked in females than in males. Age has a very slight influence on the increase. There is no direct connexion between it and the species of parasite and intensity of infestation. There is a certain correlation with splenomegaly. Treatment in many cases reduces the index to normal, and it can act to a certain extent as an indicator of the favourable effect of treatment, but it cannot guarantee absolutely a parasitological cure.

E. D. W. Greig.

MORIN (H.), BADER (H.), MONNIER (E.) & MOREAU (P.). Sur l'hyperchlorémie globulaire des paludéens au Tonkin. [**Corpuscular Hyperchloraemia in Malaria.**]—*Bull. Soc. Path. Exot.* 1934. Feb. 14. Vol. 27. No. 2. pp. 136-140.

The chlorine content of the blood corpuscles rises during an attack of malaria.

In 9 Annamites free from malaria the chlorine in the plasma averaged 3·65 grams per litre, and in the whole blood 2·78 grams. In 9 healthy Europeans, the figures were respectively 3·56 and 2·72. The same tests were carried out on 34 Annamites and 10 Europeans during attacks of malaria, with the result that while the amount of the chlorine in the plasma was found to be unaltered, the total chlorine had increased from 2·78 to 2·98 in the Annamites, and from 2·72 to 2·98 in the Europeans. The hyperchloraemia of malaria is due therefore to an increase of chlorine in the corpuscular elements. *W. F.*

ACKERMAN (V.) & FILATOV (A.). **On the Possibility of preventing Transmission of Malaria by Blood-Transfusion. (An Experimental Study of the Bactericidity of Conserved Blood with Respect to the Plasmodium malariae.)**—*Jl. Trop. Med. & Hyg.* 1934. Feb. 15. Vol. 37. No. 4. pp. 49–57. [25 refs.]

If citrated blood is kept for 5 days at 4°–6°C. any benign tertian parasites it may contain will perish.

The authors review the published accounts of numerous accidental transmissions of disease which have occurred during blood transfusion. Malaria appears to be the most common of the diseases transmitted in this way. The authors kept citrated blood infected with *P. vivax* on ice, at a temperature of 4° to 6°C. During the first four days stained films still showed some healthy parasites, though many had become shrivelled up and extracorpuscular by the end of this period. Blood inoculated during these four days usually produced malaria. After the fourth day no parasites could be found in films, nor did the blood produce malaria when it was inoculated. At a higher temperature the parasites disappeared more quickly. The addition of minute quantities of quinine to the citrated blood did not accelerate their destruction until a concentration of 1 : 1,000 was reached. Quinine in this concentration did not hasten the occurrence of haemolysis ; this did not begin until the 12th day in the citrated blood, either with or without quinine ; In higher concentration quinine produced lysis and clotting. The therapeutic effect of transfusing blood which had been kept for ten

days was equal to that of fresh blood. *P. falciparum* did not disappear until after 5 days' storage. [*P. malariae*, in the title, apparently means malaria parasite irrespective of species.] *W. F.*

GIBBINS (E. G.). **Morphological Study of Malaria Pigment in Oocysts of Naturally Infected Anopheles.**—*Parasitology.* 1933. Dec. Vol. 25. No. 4. pp. 428–435. With 4 figs.

During his examination of anopheles in Uganda for evidence of malarial infections the author made drawings of 204 oocysts found in *Anopheles costalis, A. funestus* and *A. theileri* var. *hancocki.* In this paper he describes the characters of the pigment in the oocysts which appear to indicate the species of parasite involved.

Plasmodium vivax—yellowish or light brown and consisting of delicate rods or grains arranged as a clump, a single curved line, or several fine lines crossing one another. *Plasmodium malariae*—dark brown or black, coarse and clearly visible irregular masses and rods, usually 6 to 8 in number (occasionally up to 12) arranged in curved or straight line, a clump or rarely scattered about cyst. Under high magnification the large masses were often seen to be composed of aggregates of individual rods or granules. *P. falciparum*—black grains sometimes arranged as a curved line but more frequently as a clump. The number of grains of pigment varied, being few or absent from some cysts in heavy infections. *P. ovale*—dark brown grains 15 to 30 in number and shaped like a cocco-bacillus and arranged in two or more curved intersecting lines at centre of cyst.

A series of outline drawings depict very clearly the various characters described. *C. M. Wenyon.*

CRAIG (Charles F.). **The Nomenclature of** *Plasmodium ovale* **Stephens 1922.**—*Amer. Jl. Trop. Med.* 1933. Sept. Vol. 13. No. 5. pp. 539–542.

The author in 1900 described a peculiar form of malarial parasite which in 1926 he concluded was identical with *Plasmodium vivax* var. *minuta* Emin, 1914. Whatever EMIN's parasite may be, and there is reason to suspect that it was at least in part *P. falciparum*, it seems clear that it was not *P. ovale* Stephens, 1922, with which the author now identifies the parasite noted by him in 1900. *C. M. W.*

GUARDABASSI (M.). Sur la filtrabilité du parasite du paludisme. [**The Filterability of the Malaria Parasite.**]—*Boll. Sezione Ital., Soc. Internaz. di Microbiologia.* Milan. 1933. Dec. Vol. 5. No. 12. pp. 337–338.

The results were negative.

The author has made repeated experiments with citrated, laked and defibrinated blood in tertian and subtertian malaria, but the parasites were always held back by the filter. He has inoculated refractory animals, such as rabbits, with malarious blood and, an hour later, he has filtered the animal's blood, but the parasites did not pass the filter. He also altered the pH of the infected blood before filtration, but the result was the same [this *Bulletin*, Vol. 30, pp. 487 and 857].

W. F.

SINTON (J. A.) & MULLIGAN (H. W.). **A Critical Review of the Literature relating to the Identification of the Malarial Parasites recorded from Monkeys of the Families** *Cercopithecidae* **and** *Colobidae.*—*Records of the Malaria Survey of India.* 1932. Dec. Vol. 3. No. 2. pp. 357–380 and 1933. June. No. 3. pp. 381–444. With 35 figs. on 1 plate. [3 pages of refs.]

By collecting and examining critically the literature dealing with the malarial parasites of monkeys in the Old World the authors have rendered a signal service to those who are interested in these parasites. They say that it is difficult or impossible to reconcile the considerable morphological differences between various parasites which have been grouped in a single species. They have found it necessary to create several new varieties of existing species because it seemed that this was an essential preliminary step towards the clearing up of the confusion which exists. It is recognized that the differences may be dependent on inadequacy or inaccuracies in the original descriptions or to the fact that unrecognized mixed infections were being dealt with. The species which the authors recognize are as follows :—

1. *Plasmodium kochi* (Lav.), 1899, sens. restr. and three varieties, viz., *bouilliezi* Leger, 1922, *joyeuxi* Leger, 1928 and *macfiei* var. n. Sinton and Mulligan, 1932.
2. *Plasmodium inui* Halberstadter and Prowazek, 1907 (sens. restr.) and two varieties, viz., *cynomolgi* Mayer, 1907 and *gonderi* var. n. Sinton and Mulligan, 1932.
3. *Plasmodium knowlesi* sp. n. Sinton and Mulligan, 1932.
4. *Plasmodium semnopitheci* Knowles, 1919.

This, it is admitted, is merely a tentative classification based on the descriptions which have been given and serving a useful purpose till more accurate studies can be carried out.

Attention is drawn in an appendix to the possibility of mixed infections and the suggestion is made that the morphological variations in a single species resulting from a difference in host described by KNOWLES and DAS GUPTA (this *Bulletin*, Vol. 29, p. 701) were due to the fact that two distinct parasites (*P. knowlesi* and *P. inui* var. *cynomolgi*) were involved. Experimental evidence in support of this suggestion is given. The characters of *P. knowlesi* as seen in pure infections are illustrated in a plate. It is pointed out that the monkey in which KNOWLES and DAS GUPTA first saw the malarial parasites studied by them was identified as *Cercopithecus pygerythrus*. This appears to have been an error, the monkey actually being *Silenus irus* (*Macacus cynomolgus*). The natural host, therefore, of *P. knowlesi* is this monkey and not the African one. It is stated in a footnote that the sporogony cycle of *Plasmodium inui* var. *cynomolgi* has been obtained in a number of anopheles, sporozoites having been found in the salivary glands of *A. annularis* (*A. fuliginosus*), *A. splendidus* (*A. maculipalpis*), *A. maculatus* and *A. culicifacies*. The infection was actually transmitted to a *S. rhesus* by the bite of *A. annularis*. This anopheles has also been infected with *P. knowlesi*. *C. M. Wenyon.*

SCHWETZ (J.). Sur une infection malarienne triple d'un chimpanzé. [**A Triple Malarial Infection in a Chimpanzee.**]—*Zent. f. Bakt.* 1. Abt. Orig. 1933. Nov. 1. Vol. 130. No. 1/2. pp. 105–110. With 1 coloured plate.

In the blood of a chimpanzee about a year old which had been captured in the forests a hundred miles from Stanleyville and sent to

the laboratory at this place, malarial parasites were discovered. The animal was kept under observation for three months during which not only did the intensity of the malarial infection vary, but also the character of the parasites. It appeared that there was a triple infection of *Plasmodium falciparum*, *P. vivax* and *P. malariae*, the proportion of each varying from time to time. On one occasion a trypanosome was seen in the blood and on several occasions microfilariae. The chimpanzee did not appear to be in ill health as a result of the various infections. A beautiful coloured plate of 34 infected red cells shows the types of malarial parasite encountered. *C. M. W.*

SCHWETZ (J.). Contribution à l'étude des parasites malariens (Plasmodium) des singes inférieurs africains. [**Malaria Parasites of African Monkeys.**]—*Zent. f. Bakt.* I. Abt. Orig. 1933. Nov. 1. Vol. 130. No. 1/2. pp. 111–120. With 3 figs. & 2 coloured plates.

The author has found that monkeys in the Belgian Congo belonging to various genera (*Cercopithecus*, *Cercocebus*, *Colobus*, *Cynocephalus*) are commonly infected with a malarial parasite of uniform morphology.

The young rings resemble those of *Plasmodium falciparum*, but as growth occurs they take on the character of *P. vivax*, though the red cells are only rarely enlarged and that slightly, while Schüffner's dots do not occur. No pigment could be found in any of the asexual forms though the male and female gametocytes contained large quantities of yellow brown pigment. The asexual forms showed no sign of preparation for division in nuclear multiplication and no mature schizonts were seen, but in the bone marrow smear of one heavily infected monkey forms like the schizonts of a species of *Theileria* were found. Whether these are related to the malarial parasite was not determined. The parasite, illustrated in a coloured plate in its various forms, differs from the descriptions which have been given for *P. kochi* and *P. inui*. In view of its peculiar characters the author wonders if the parasite actually belongs to the genus *Plasmodium*. *C. M. W.*

MULLIGAN (H. W.) & SINTON (J. A.). **Studies in Immunity in Malaria. Part III. Multiple Superinfections with Various Strains of** *Plasmodium knowlesi*.—*Records of the Malaria Survey of India.* 1933. Dec. Vol. 3. No. 4. pp. 809–839. [10 refs.]

Infection and re-infection of *S. irus* with several different strains of *P. knowlesi* may render it immune to some other strains, but will not render it immune to all [see this *Bulletin*, Vol. 30, p. 831].

The authors here describe further experiments in immunity as studied with strains of *P. knowlesi* isolated from seven different specimens of *Silenus irus* (*Macacus cynomolgus*, *Macacus fascicularis*, the crab-eating macaque of Burma, Siam, and the Malay Peninsula). The object of these experiments was to determine if superinfection with a number of strains would render monkeys immune to all strains. If this should prove not to be the case, doubt would be thrown on the value of "salted" labour when employed in places far removed from the districts in which it was recruited. The monkeys used in the experiments were *S. rhesus*, and infection was conveyed by blood inoculation. A chronic or latent infection with one strain of *P. knowlesi* protected the monkey against further inoculations of the same strain; these were sometimes followed by an increase in parasites, but never by clinical

symptoms. Inoculation with one strain did not protect against another, unless it happened that they shared some antigenic component. Repeated inoculation with several different strains did not insure immunity to all. For example, a rhesus monkey was inoculated with a strain C, and had a very severe attack followed by a chronic infection with occasional parasites which were found up to the 310th day. It was superinfected on the 343rd day with strain K1 and suffered a moderately acute attack. It was inoculated with other heterologous strains, K2, K3, and K4, on the 379th, 427th and 484th days respectively. The results of these last three inoculations were much less severe, possibly these strains contained some antigenic components present in the strains previously injected ; but universal immunity to all strains of *P. knowlesi* had not been attained in spite of the long period of infection and the multiplicity of the infecting strains, for inoculation of another strain, K6, on the 523rd day, produced a very severe infection from which the animal died on the 529th day. *W. F.*

KRISHNAN (K. V.), SMITH (R. O. A.) & LAL (Chiranji). **Contributions to Protozoal Immunity. Part II. Immunity to Malaria in Monkeys and the Effect of Splenectomy on it.**—*Indian Jl. Med. Res.* 1934. Jan. Vol. 21. No. 3. pp. 639–647. [15 refs.]

Acquired immunity to malaria in monkeys is generally, but not always, due to latent infection.

The ordinary course of the disease in *Macacus* (*S.*) *rhesus* inoculated with *Plasmodium knowlesi* was as follows :—A primary acute attack, treated with quinine, lasted from 4 to 10 days. A second short period of about the same length followed, with no parasites and no treatment. Next came a third period of 4 to 8 weeks duration characterized by relapses which were treated with quinine whenever the parasites numbered more than five per microscopic field. This was followed by a fourth period lasting for months, during which the animal appeared to be in good health and no parasities were found in the peripheral blood. The monkey now possessed a high degree of acquired immunity to re-inoculation of infective material [? the same strain of parasite] ; but, if the spleen were removed, an intense infection resulted which showed that the immunity was associated with a latent infection. The above procedure is recommended as an economical method of maintaining a strain of monkey plasmodium in the laboratory. The presence of dividing monocytes [? in films made from spleen-puncture] appears to indicate latent infection and immunity. Although acquired immunity is usually due to latent infection, there is some indication that in a small percentage of monkeys it may be present in the absence of any such infection, this applies particularly to *irus* and *radiatus* monkeys. *W. F.*

WATS (R. C.) & GUPTA (B. M. Das). **Comparative Biochemical Findings in Blood of Normal and Malaria-infected Monkeys.**—*Indian Jl. Med. Res.* 1934. Jan. Vol. 21. No. 3. pp. 475–481. [13 refs.]

The authors found no noteworthy changes in the blood-sugar, non-protein nitrogen, or calcium in monkey malaria. No marked increase of inorganic phosphates occurred in untreated cases, but there was a rise in animals treated with quinine or atebrin. The cholesterol of the plasma was lowered. *W. F.*

HUFF (Clay G.). **Comparative Studies on Susceptible and Insusceptible** *Culex pipiens* **in Relation to Infections with** *Plasmodium cathemerium* **and** *P. relictum.*—*Amer. Jl. Hyg.* 1934. Jan. Vol. 19. No. 1. pp. 123–147. With 2 text figs. and 20 figs. on 2 plates. [16 refs.]

A study of the development of *Plasmodium cathemerium* and *P. relictum* in *Culex pipiens* with a view to determining if there was any difference in the stomach of susceptible and insusceptible mosquitoes.

The mosquitoes were fed twice at an interval of 5 days on birds infected to such a degree that each ingested from 53,000 to 26,000 gametocytes. Of 80 fed upon birds with *P. cathemerium* infection 43 showed normal parasites from both feeds while 30 had no parasites. Similarly, of 57 ingesting *P. relictum* 23 were infected from both feeds while 32 failed to become infected. The 9 remaining failed to show parasites from one feed but it is thought that those from the other feed may have been overlooked. The stomachs were examined by serial section. As regards the histology of the blood meal and the surface epithelium there was no difference between the susceptible and the insusceptible mosquitoes. Normal and degenerating zygotes were found in both for about 30 hours, the number of normal zygotes decreasing in general with the passage of time. After about 18 hours oocysts began to appear on the outer surface of the stomach in susceptible mosquitoes. In the stomach degenerating zygotes were regularly present from 12 to 30 hours and irregularly up to 68 hours. No evidence of a cellular response to invasion by the parasite could be detected. Penetration of the epithelial lining of the stomach was by a gradual sinking of the parasite between two cells. In no case was there any evidence of an active boring into a cell or between the cells. In the process the long axis of the parasite was parallel to the surface of the stomach.

The conclusion is that as no visible difference between the susceptible and insusceptible mosquitoes could be detected it would seem that the difference must be a biochemical one involving possibly enzymes or humoral parasiticidal substances. Incidentally a study of black spores within oocysts of all ages was carried out. All stages in the altering of sporozoites were followed, from an initial yellowing and thickening till they were no longer recognizable as such but appeared as large dark brown bent or twisted structures. The author's view is that the change is due to chitinization, possibly as a result of invasion of the oocysts by very fine tracheoles. *C. M. Wenyon.*

HECHT (Otto). Experimentelle Beiträge zur Biologie der Stechmücken V. Ueber den Wärmesinn der *Anopheles maculipennis*-Rassen bei der Eiablage. [**Heat-Sense of** *A. maculipennis* **Races in Deposit of their Eggs.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1934. Mar. Vol. 38. No. 3. pp. 124–131. With 1 fig.

Different races of *Anopheles maculipennis* are found in different parts of Europe, and one of them is said to favour cold water. Is it possible to find a physiological explanation of the differences in geographical distribution?

The author has taken females of different races, laying eggs distinguishable by colour and pattern, and given them opportunities of laying eggs in vessels kept at different temperatures. He has repeated his experiments again and again at different seasons, using many

mosquitoes, and recording the laying of tens of thousands of eggs. His results show conclusively that females which lay "dark" and "banded" eggs exercise no choice at high temperatures, for instance between water at 34°C. and at 28°C. But if the choice is between cooler waters (29° and 19°C.) the "dark" eggs are placed indiscriminately, but the "banded" eggs are nearly all in the warmer vessel. At a lower pair of temperatures (25° and 18°C.) this limitation of the banded eggs becomes clearer still.

Once again the physiologist has systematized a number of field observations, of which he has provided a clear and single explanation.

P. A. Buxton.

WEYER (Fritz.) Beobachtungen an Hausanophelen im Zusammenhang mit der Rassenfrage bei *Anopheles maculipennis*. [**Observations on House Anopheles in connexion with the Racial Question in** *A. maculipennis*.]—*Ztschr. f. Parasitenk.* 1933. Dec. 18. Vol. 6. No. 3. pp. 288–307. [24 refs.]

ROUBAUD's theory of zoophily and androphily, as respectively characteristic of the two races of *A. maculipennis*, received no support from the author's investigations, conducted in a large *atroparvus*-area in E. Friesland, the only part of Germany where malaria is endemic.

Not only the race or variety mentioned, but also var. *messeae* was found to suck both human and animal blood, and it has been shown experimentally that both races are equally susceptible to malarial infection. It would seem, then, that the true explanation of the diminution and present day distribution of malaria in Europe, or in other words of "anophelism without malaria," has yet to be found. In the area investigated Anopheles in houses were very few in number in comparison with those captured in occupied cowsheds, pigsties and stables, where both races occur more abundantly, although they also enter houses. Possibly the presence of the non-malaria-carrying var. *messeae* in bedrooms is explicable on MARTINI's hypothesis that, after feeding, the insects seek out places where the temperature is below 16°C., so that the development of plasmodia becomes impossible.

E. E. Austen.

SAUTET (Jacques). Contribution à l'étude de l'*Anopheles maculipennis* en Corse. Gîtes d'été et gîtes d'hiver, dans leurs rapports avec le paludisme. [*A. maculipennis* **in Corsica : Summer and Winter Haunts in Relation to Malaria.**]—*Ann. Parasit. Humaine et Comparée.* 1934. Jan. 1. Vol. 12. No. 1. pp. 8–14. With 1 fig.

In the warm eastern plain of Corsica, the summer and winter haunts of *A. maculipennis* are often very different. The former are divisible into feeding places and such as are associated with the hatching-out of adults and oviposition, and in both the proportions of the sexes show marked disparity. The winter haunts, on the other hand, while sometimes the same as those of summer, frequently consist for the most part of unoccupied premises or cavities. Here, however, the mosquito bites readily, if disturbed by man, and so may occasionally transmit malaria at this season. There is thus in Corsica a homodynamous race, with all the characteristics to which ROUBAUD and the Dutch authors

have drawn attention, though here a mosquito, which is chiefly domestic in summer, frequently tends to behave like a " wild " species in winter, and very differently from the way in which it comports itself in Holland, where, as shown by SWELLENGREBEL, human dwellings form its places of winter concentration. Thus the biology of the same species of Anopheles, or even of the same race, may differ very greatly in different countries, and this very often explains the apparent contradictions in the regional epidemiology of malaria. *E. E. A.*

i. TOUMANOFF (C.). Recherches sur la fréquence saisonnière de diverses espèces anophéliennes au Tonkin (Bassin du Fleuve-Rouge). 3e Note : *A.* (*Neocellia*) *maculatus* (Théo.). [**Seasonal Frequency of Various Species of Anophelines in Tonking (Red River Basin).**]—*Bull. Soc. Path. Exot.* 1933. Oct. 11. Vol. 26. No. 8. pp. 1020–1022. With 1 fig.

ii. ——. Quatrième note: *A.* (*Neocellia*) *fuliginosus* Giles, *A.* (*Neocellia*) *maculipalpis* var. *indiensis* James et Liston, *A.* (*Neocellia*) *philippinensis* Lüdl.—*Ibid.* Nov. 8. No. 9. pp. 1167–1171.

i. In Tonking, the seasonal frequency of *Anopheles maculatus* coincides with that of *A. minimus* (*ante*, p. 55), whose breeding places it frequently shares. The abundance of both species during the winter monsoon is of special significance in connexion with the severity of the incidence of malaria in the middle and upper regions of the Red River basin.

ii. While two years' investigation of the species of the *Neocellia* group in Tonking proved not altogether conclusive, it appears that the seasonal abundance of these anophelines is never so marked as is that of members of other groups (*Anopheles minimus*, *A. aconitus* and *A. vagus*), or of *A. maculatus*. *A. fuliginosus* and *A. philippinensis* are apparently summer monsoon species, which are scarce in the second portion of the winter monsoon. *A. maculipalpis*, which showed a slight increase in numbers during the intermediate seasons (April and October), was, at least in the larval stage, moderately abundant at other times. *E. E. A.*

MORIN (Henry G. S.) & BADER (H.). Recherches sur quelques facteurs physico-chimiques de l'oecologie des larves d'anophèles au Tonkin. [**Physico-Chemical Factors in the Ecology of Anopheline Larvae in Tonking.**]—*Ann. Inst. Pasteur.* 1933. Nov. Vol. 51. No. 5. pp. 656–668. With 1 map in text.

In Indo-China hilly regions are more malarious than low-lying deltas, since *Anopheles minimus*, *A. maculatus* and *A. jeyporiensis*, the principal local vectors, breed almost exclusively in clean running water. The object of the investigations summarized in the present paper was to determine whether the chemical composition of the waters in the unhealthy region includes some common feature distinguishing them from those in the healthy zone. The data obtained showed much seasonal variation, so that for their full interpretation more prolonged research is necessary.

As already shown by a number of other workers, the majority of Anophelines are relatively tolerant of fairly considerable variations in

pH ; and a high degree of mineralization is not *per se* and invariably an obstacle to breeding. On the other hand the determining favourable factor appeared to be the presence in the water of a certain quantity of CO_2 gas in a state of free solution. The term "carbonic index" is introduced for the figure representing, in milligrammes of CO_2 per litre for a given sample of water, the excess of free and half-dissolved carbonic acid over the potential CO_2 content, the method of determining which is described.

During two years from March 1931, more than four hundred samples of water from different sources were examined ; the purest, such as those from springs in the upper region, were found to have the highest indexes, while in the dry season stagnant water from pools in the low-lying delta proved practically negative in this respect. Springs and rapid streams are the chief centres of Anopheles-breeding in Tonking ; these have a high carbonic index, and there is thus a curious parallelism in this respect. Should it prove that seasonal variations in the carbonic index affect the predominance or the reverse of a given malaria-carrying species, a factor of probable importance in particular outbreaks of the disease would have been discovered, and might perhaps in certain cases be modified. *E. E. A.*

DE MEILLON (B.). **Distribution of** *A. gambiae* **and** *A. funestus.—Union of South Africa. Ann. Rep. Dept. of Public Health Year ended 30th June, 1933.* Annexure D. pp. 61–64.

This excellent report is a summary of the author's findings.

A. funestus breeds in the permanent streams which have their origin in the Drakensberg. The population of this species is therefore stable, and this is reflected by the intensity of malaria where it predominates, as well as by the absence of epidemics. *A. gambiae,* in direct contrast, shows great fluctuations which depend on the rainfall, because it breeds in small temporary pools. When there is an abnormally heavy rainfall, epidemics of malaria arise in districts where the disease is rarely seen and where anopheles are seldom found. In South Africa epidemics of malaria are always associated with *A. gambiae.* In dry weather this species breeds in quiet, exposed backwaters of rivers ; *A. funestus* breeds in shaded portions where there is a current. The prevalent idea that the larvae of *A. gambiae* can resist desiccation in dried mud is not correct. This mosquito is not a frequenter of houses to the same extent as *A. funestus*, it shelters under damp stones, in crevices and hollows.

A. funestus is a house frequenter. One which enters a house with its eggs undeveloped remains there until they are ripe, and in the meantime it feeds repeatedly. This explains the high rate of infection in this species. It feeds indoors, not out of doors. Above 2,500 feet, its habits change. Though larvae are numerous up to 3,500 feet, the mosquitoes do not enter houses, and there is no malaria (see ROUBAUD *ante,* p. 424). As regards range of flight, 80 per cent. of this species remain within a half-mile radius, but both males and females may occur as far as two miles from their point of origin. The author has recorded a flight of 4½ miles when no nearer source of human blood was available.

Spraying a hut with insecticide at 8 p.m. did not prevent anopheles entering in the early morning. An application of citronella is not sufficient to last all night, its repellent effect passes off in about 5 hours.

W. F.

SCHAPIRO (Louis). **Observations and Experiments on Mosquito Breeding in Pit Latrines in Panama.**—*Amer. Jl. Hyg.* 1934. Jan. Vol. 19. No. 1. pp. 254–259.

To test whether pit latrines, which, as employed in Panama, play an important part in the campaign against ankylostomiasis, are breeding places of Anopheles and thus concerned in the spread of malaria, twenty-six such latrines in La Chorrera and other cities were inspected. Anopheles were not found.

All but one were in use, and the majority from a quarter to half full of water. The mosquitoes collected, either emerging from the pits or on the walls, included specimens of seven species of Culicines, but not a single Anopheles. The results of an attempt to breed out larvae of the latter genus, placed under laboratory conditions in dilutions of faeces of various strengths, were not altogether conclusive. Those in strong dilutions perished within 48 hours ; with three exceptions, in which all larvae died, those in weaker dilutions lived longer and, except in one instance, gave rise to a varying percentage of adults. It is concluded that " the pit latrines used in Panama are not important breeding places for *Anopheles* mosquitoes." According to a footnote, it has been found by experience that " six ounces of diesel oil applied every ten days to a latrine pit 2 feet long by 3 feet wide by 10 feet deep effectively controls mosquito breeding." *E. E. Austen.*

PAVLOVA (P. I.). **Artificial Alteration of the Active Reaction of Water Reservoirs for the Control of the Larvae of the Malaria Mosquito.**—*Med. Parasit. & Parasitic Dis.* Moscow. 1932. Vol. 1. No. 5–6. pp. 265–266. [In Russian.] [Summarized in *Rev. Applied Entom.* Ser. B. 1934. Feb. Vol. 22. Pt. 2. p. 21.]

" In the summer of 1930, field experiments were carried out near Moscow on the control of Anopheline larvae [*Anopheles maculipennis*, Mg.] in pits in peat-bogs, etc., by modifying the hydrogen-ion concentration of the water and comparing the results with those obtained with oil and Paris green. The larvae were destroyed when the pH of the water in the pits was reduced to 1·9 by the addition of sulphuric acid, and this figure was approximately maintained for about two months in pits with a clay bed. In those having a sedge-peat bed, however, the action of the acid was neutralised in a comparatively short time by the alkaline reaction of the peat, after which the mosquito larvae again occurred."

BEKLEMISHEV (V. N.). **Whence come Adult Anophelines in Areas that have been subjected to Avio-Chemical Treatment?**—*Med. Parasit. & Parasitic Dis.* Moscow. 1933. Vol. 2. No. 1–2. pp. 53–59. With 1 graph. [In Russian.] [Summarized in *Rev. Applied Entom.* Ser. B. 1934. Feb. Vol. 22. Pt. 2. p. 37.]

" In a rice-growing area to the north of Lake Balkash in south-eastern Kazakstan, Paris green was applied by aeroplane to all the rice-fields and adjoining marshes, etc., at intervals throughout the summer of 1932 for the control of *Anopheles maculipennis*, Mg. In August, however, adults of this mosquito were present in all villages, though no larvae could be found. The mosquitos were most numerous in the houses nearest to the rice-fields, and so had almost certainly not come from some other breeding-place that had been overlooked during the

dusting operations. The preceding applications of dust had been made on 19th July and 10th August, and by calculating the duration of the life-cycle of the mosquito in comparison with the average temperature of the water, it was evident that a generation had matured in the interval, the pupae being unaffected by the dust. The maximum duration of the life of the females in August in this district was found to be 20 days. In a neighbouring district where dust applications in August had been correlated with larval development, hardly any adult Anophelines occurred from September to the end of the year. In districts where control was not applied, the mosquitos were abundant in houses in September and malaria was severe. It is concluded that the position of breeding-places can be determined from the places in which adult mosquitos are found in the day-time."

MORIN (Henry G. S.) with the collaboration of P. MARTIN. Possibilités d'utilisation pratique du vert de Paris en Indochine. [**The Use of Paris Green in Indo-China.**]—*Arch. Insts. Pasteur d'Indochine.* 1933. Apr. No. 17. pp. 103–140. With 4 plates (2 folding). [49 refs.]

The author prefers oil to Paris green as a larvicide in Indo-China, where anopheline breeding and malaria are continuous throughout the year, and the labourers available are quite uneducated.

The author deals first with the principles of the use of Paris green, which is aceto-arsenite of copper, a by-product of various metallurgical industries. It should be completely soluble in ammonia, and should contain from 50 to 55 per cent. of arsenious anhydride. As it is insoluble in water, it must be fine enough to pass into the digestive tubes of the larvae, and light enough to float on the surface of the water where they feed. The mouthless pupae and the minute first and second stage larvae which are too small to swallow it are unaffected by Paris green. The author employed a 1 per cent. mixture, and he found that the most effective diluent in Indo-China consisted of 9 parts of road dust with 1 part of powdered wood charcoal; this diluent itself was lethal to larvae. It is one of the advantages of Paris green that it can be applied to extensive lakes, marshes, and flooded areas without the clearing away of weeds and algae, which is a necessary preliminary to the application of oil. Paris green when applied to water in the proportion of 1 litre of a 1 per cent. mixture to 100 square metres of surface, does not make the water poisonous, either for the animals which drink it or for the fish which live in it. It is transformed by contact with the flora of the water into volatile ethylarsine, and, consequently, successive applications produce no accumulation of arsenic. For a man to consume the minimal fatal dose of 0·005 grams of arsenic, it would be necessary for him to swallow 240 litres of the treated water, or to eat 44 kilograms of the fish caught in it. The labourers who apply the Paris green should wear special clothes while at work, and should change and wash before eating. They should never touch the undiluted powder with bare hands. Anyone found, by the occurrence of eczema, to be particularly susceptible to arsenic should be taken off the work.

One of the disadvantages of Paris green is the difficulty of checking its application, for, unlike oil, it leaves no visible film, and its traces in the water are so minute as to defy detection by ordinary chemical means. According to HACKETT, a few cubic centimetres of the treated

water give off a characteristic smell of garlic if they are added to a culture of *Penicillium brevicaule.*

Oiling is the method of larval control generally adopted in Indo-China, and the author doubts whether Paris green is as suitable in a country where malaria is not an affair of seasons but is continuous from year's end to year's end. Any disturbance of the water causes the Paris green to sink, and, should it rain within 5 hours of its distribution, it must be re-applied. Another objection which he raises is that the labour available is neither sufficiently educated nor sufficiently trustworthy to handle a poisonous substance with efficiency and safety.

The distribution of Paris green by an aeroplane has been found efficacious in the case of an aviation camp at Tong, and the author thinks that this method may be very useful for protecting temporary concentrations of soldiers on active service, or possibly as an immediate preliminary measure under other conditions. *W. F.*

MORIN (Henry G.), BADER (H.) & MARTIN (P.). Sur le mode d'action larvicide du vert de Paris. [**How Paris Green acts.**]—*Bull. Soc. Path. Exot.* 1933. Dec. 13. Vol. 26. No. 10. pp. 1267–1273.

Paris green contains arsenites and arsenates. The arsenites are more important. A method of assay is given.

The larvicidal properties of Paris green are due to the arsenic which it contains. But this is present in two forms the arsenite and the arsenate of copper. Arsenites are slightly more toxic than arsenates for man, and the authors have carried out experiments with larvae which show that the arsenites are much the more powerful form for destroying anopheline larvae. The usual method of determining the arsenic content of Paris green in terms of the trioxide is therefore insufficient. The authors give details of a method by which the arsenite content can be determined. *W. F.*

MACKAY (R.), BUCHANAN (J. C. R.) & SANDERSON (I.). **Arsenical Poisoning associated with Larvicidal Treatment of Water with Paris Green.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1934. Mar. 12. Vol. 27. No. 5. pp. 517–523.

Paris green applied in the usual way caused an outbreak of arsenical poisoning among the Tanganyika natives who used the treated water.

The authors note the rarity of recorded poisoning after the use of Paris green and the similarity of the symptoms to those of some dietetic deficiency. Their treatment of eight water-holes and a weed-covered pool once a week over a period of 3 months resulted in the illness of 132 persons.

The green was stated to contain 55·37 per cent. arsenious oxide and 1 per cent. water soluble arsenic. It was at first applied by blower, then by hand, a handful of the one per cent. mixture with powdered red earth and sand being dusted over each water-hole, 5–8 feet in diameter [depth is not stated].

Symptoms appeared after a minimum period of 3–5 weeks, but their significance was not at first appreciated. They were in order of relative frequency.

"A sensation of burning and tingling in the soles of the feet, generalised itching of the skin, paraesthesias of the palms similar to those felt in the feet, pains in the limbs, abdominal pain, diarrhoea, burning and watering

of the eyes, oedemas and, in one case, fever. These, in a variety of combinations, made up the clinical picture of the milder cases, and to them were added later desquamation, paresis, keratosis, bronchial affections, herpes and lastly, but fortunately rarely, paralysis."

These symptoms are then discussed, burning feet as the commonest indication of something wrong; intense itching of the skin as the first symptom in 20 per cent.; gastro-intestinal disorders as not prominent; oedema with pitting over the tibiae in 15 per cent.; desquamation beginning about the third week, and at times so severe as to merit the term exfoliation and giving a striking appearance to the natives not unlike the depigmentation of mycotic infections; paresis in the extensors of arms and legs in 9 per cent. Arsenic was readily detected in the urine, as also in water from the water-holes a week after the last application. *A. G. B.*

HACKETT (L. W.). **Arsenical Poisoning with Paris Green.** [Correspondence.]—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1934. May 9. Vol. 27. No. 6. p. 628.

Commenting upon the above paper Dr. Hackett writes that no one with any experience would dare to recommend the hand-dusting of Paris green on small collections of water used for domestic purposes; blowers should be used because only in this way can the proper dose (1–2 decigrams per sq. met.) be applied. Tons of the green are being used every summer in Italy and other Mediterranean countries and no word of poisoning of man or beast has reached Hackett. The incident described by MACKAY *et al.* is probably due "to carelessness in throwing about a poisonous substance without scientific control of the dosage."

A. G. B.

BOETTGER (Caesar R.). Ueber die Artzugehörigkeit des in Italien zur Malariabekämpfung eingeführten Zahnkärpflings. [**Species of the Gambusia introduced into Italy in the Antimalarial Campaign.**]—Reprinted from *Zool. Anzeiger.* 1933. Vol. 105. No. 1/2. 14 pp. [21 refs.]

There are three species of Gambusia in U.S.A.: an easterly species, *holbrooki*, on the rivers which flow to the Atlantic, a central, *patruelis*, on the Mississippi system, and a western, *affinis*, in Texas. The author reaches the conclusion that for the species introduced into Italy the name *Gambusia holbrooki* Girard should be replaced by *G. patruelis* Baird and Girard. A useful list of references is appended. *A. G. B.*

PRENDEL' (A. R.), ZAGOROVSKIĬ (N. A.) & FUTRAN (G. S.). **Data on the Acclimatisation of *Gambusia* in the U.S.S.R.**—*Med. Parasit. & Parasitic Dis.* Moscow. 1932. Vol. 1. No. 5–6. pp. 261–264. [10 refs.] [In Russian.] [Summarized in *Rev. Applied Entom.* Ser. B. 1934. Feb. Vol. 22. Pt. 2. pp. 20–21.]

"An account is given of observations in Odessa in 1930–32 to determine whether *Gambusia* can thrive under the climatic conditions of southern Ukraine. Notes on its biology are included. It was found that the fish can survive the winter (in a pond in which the water was covered with ice for 3½ months), and multiply in large numbers during the summer and autumn without being given artificial food. They

lived for several months in water the salinity of which was gradually increased from 0·5 to 1·5 per cent., but died in a few days in water containing 2 per cent. NaCl. They also lived in naturally brackish water in drainage ditches, in which the salt content did not exceed 0·6 per cent. This power of adaptation to brackish water is of special importance on the north-western coast of the Black Sea, where the stagnant water in which mosquitos breed in spring often becomes brackish in summer."

YOUNG (T.). **Quinine Prophylaxis in Northern India.**—*Jl. Roy. Army Med. Corps.* 1933. Aug., Sept., Oct., Nov. & Dec. Vol. 61. Nos. 2, 3, 4, 5 & 6. pp. 90–98; 180–184; 262–267; 330–339; 412–426. With 1 chart. [54 refs.]

These experiments demonstrate the value of quinine prophylaxis in a country where the malaria season is limited to a short period of about 8 weeks in the year.

The observations were made in Nowshera for the first two years, and were subsequently extended to other districts. The period of infection in Nowshera begins in the middle of September and ends in the first week of November. The same is more or less true of the other stations to which the experiment was extended. In ordinary years malaria is mainly benign tertian, but when epidemics occur, subtertian is more common. The dose of quinine employed for prophylaxis was ten grains of the sulphate in solution every evening, except Saturday evening, for three weeks. In 1926, this treatment was given to the English troops at Nowshera from October 4 to 24. The quinine group consisted of 210 men; during October, there were 17 cases among them, or 81 per thousand. In the control group of 225 men, there were 68 cases, or 302 per thousand.

In 1927, both British and Indian troops were treated, and two courses of three weeks each were given, with a ten days' interval between them. The results were as follows:—In the British quinine group consisting of 194 men, there were 6 cases or 31 per thousand; in the control group of 270 men there were 26 cases, or 96 per thousand. In the Indian quinine group of 443 men there were no cases of malaria, and in the control group of 441 there were only 9 cases.

In 1928, other units in Peshawar were included. In cantonments, there was so little malaria that the test was of no value; but in the Chitral Relief Column, the quinine group which was about 500 strong had 3 cases of malaria, while the control group, consisting of some 3,200 men, had 83 cases.

The year 1929 was the worst malaria year in the records of the district. Among 473 British troops on quinine, the incidence of malaria was 2 per thousand during the first 3 weeks' course and 142 per thousand during the second. In the control group of 228 men, it was 39 during the first period and 211 in the second. During the six weeks after the quinine had been stopped, the incidence in the two groups was approximately equal. With Indian troops the prophylactic treatment was equally successful and the amount of malaria among those taking quinine was considerably less than among those forming the control.

"Throughout all stages of the experiment there was a definitely reduced incidence of malaria and a definitely lower ratio of admissions to hospital for all causes among those taking quinine." The cost of the quinine was a little less than one rupee per man. Apart from its

taste, the treatment was popular. The bitter taste is a serious obstacle in the way of efficient prophylactic treatment, and tablets were substituted with satisfactory results in the case of the Chitral Relief Force. [The tablets made by responsible firms are quite trustworthy; as an alternative gelatine capsules may be used.] No ill effects attributable to quinine were noticed during the course of the experiment. The 10 days interval between the two courses has now been found unnecessary and has been abandoned. The author concludes that in non-epidemic years the prophylactic treatment is hardly worth the cost and labour involved, but in epidemic years the outlay is amply repaid. He intended to continue the experiments in 1930, but the authorities refused to allow the use of controls, on the ground that the case for quinine prophylaxis had been completely proved, and orders were received to issue 10 grains of quinine, 5 days a week, for ten weeks, from the beginning of September to the middle of November, to all troops in malarious stations. *W. F.*

MISSIROLI (A.) & MARINO (P.). Anwendung des Chinoplasmin zur Malariasanierung. [**Quinoplasmoquine in Malaria Control.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1934. Jan. Vol. 38. No. 1. pp. 1–16. With 8 figs.

Observations made in a hyperendemic malaria area in Sardinia to determine the value of quinoplasmoquine in controlling malaria.

The place selected was Torpé, Sardinia, a district of 1,200 inhabitants, in which the malaria was hyperendemic, as determined by the spleen and parasite index. The dose of plasmoquine was 2 cgm. for adults with reduced doses for younger persons; it was given as quinoplasmoquine (quinine 0·3 gm., plasmoquine 0·01 gm.), as the quinine would act on the schizonts, whilst the plasmoquine acted on the gametocytes. The entire population received plasmoquine for 10 days in April and in June. During the course of the treatment cases of the following occurred:—Blackwater fever 1, jaundice 9, gastralgia 14, metrorrhagia 3, fainting 7. It was not possible to say whether the blackwater fever was caused by the quinine or the plasmoquine. The authors refer to the work of BARBER, KOMP and NEWMAN [this *Bulletin*, Vol. 26, p. 939] on the effect of small doses of plasmoquine in preventing infection of anopheles, and they have developed it further. [They do not refer to the work of CLEMESHA and MOORE [*loc. cit.*, Vol. 28, p. 576], who reach the conclusion, after 5 years experience of anti-malarial measures on Travancore Tea Estates, that anti-gametocyte campaigns with quinoplasmoquine can be easily carried out with success on estates, but that "*such a thing is practically hopeless with a civil population.*"] As a result of their investigations in a hyperendemic malaria area in Sardinia the authors reach the following conclusions:—(1) The administration of plasmoquine in 2 cgm. doses for adults and proportionately smaller doses according to age, in the form of quinoplasmoquine, given every second day to the entire population of an agricultural area of Sardinia, proved harmless. (2) During the period of treatment the percentage of infected anopheles fell to zero; in the control area it rose to over 2 per cent. (3) During the same period the incidence of malaria in the villages treated with plasmoquine fell markedly. (4) Treatment for 10 to 20 days with plasmoquine during the pre-epidemic period showed no effect on the course of the subsequent epidemic.

E. D. W. Greig.

SOESILO (R.). **Atebrin in Malaria Prophylaxis. Preliminary Report.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1934. Jan. 31. Vol. 27. No. 4. pp. 421–423.

—— & GILBERT (A. Ph. W.). Over causale prophylaxis en therapie met atebrin (tweede mededeeling). [**Causal Prophylaxis and Therapy with Atebrin. II.**]—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1934. Feb. 27. Vol. 74. No. 5. pp. 271–273.

The definitely prophylactic results obtained with atebrin were :—

(*a*) Twenty-one volunteers in Java, prophylactically treated with 0·1 or 0·2 grams of atebrin, were bitten 5 or 24 hours later by mosquitoes infected with tertian malaria. Six of them developed parasitaemia in 12 to 24 days with fever in 15 to 24 days. The remaining fifteen showed no sign of infection for 14 months, the period of their observation.

(*b*) Ten out of 11 control persons, who had received no atebrin had parasites in their blood in 8 to 13 days and fever 10 to 14 days after being bitten.

The trials of curative treatment were carried out on 17 volunteers infected with malaria with a dosage of one 100-mgm. tablet thrice daily for 5 to 6 days. Four persons began treatment before the temperature had risen and thirteen after. The preliminary report gives the results of observation over a period of 8 months, and the second communication extends this period to 12 to 17 months. The results were :—

(*a*) Fourteen persons showed neither schizonts nor gametes.

(*b*) One of the treated developed parasitaemia and pyrexia in about 2 months. A second showed parasites again 36 days after cure. A third developed parasitaemia and fever one year after treatment.

Naturally acquired tertian malaria was also treated in 6 cases with the same dosage of atebrin for 5 days. After 3 days use of atebrin schizonts and gametes disappeared. Five patients have remained for 12 months after the last atebrin dose free of malaria. The sixth developed malaria relapse 9 weeks after the treatment but has since remained free. *W. F. Harvey.*

KASSIRSKY (J. A.), BUROWA (C. F.) & UMIDOWA (S. J.). Beiträge zum Studium des Zirkulationssystems bei der Malaria. [**Circulatory System in Malaria.**]—*Arch. f. Schiffs- u. Trop.-Hyg.* 1934. Feb. Vol. 38. No. 2. pp. 66–74. With 8 figs.

A clinical study of the effects of malaria on the circulatory system as seen in cases in central Asia. In all 45 cases were studied.

E. D. W. Greig.

LAJOS (S.). Ueber die Anwendung des Atebrin bei Malaria tertiana. [**Atebrin in Tertian Malaria.**]—*Muench. Med. Woch.* 1934. Jan. 5. Vol. 81. No. 1. p. 22.

Describes the treatment of three cases in Hungary. *A. G. B.*

SCHWETZ (J.), BAUMANN (H.), PEEL & DROESHAUT. Sur la proportion des trois espèces malariennes trouvées chez les enfants noirs de la consultation des nourrissons à Stanleyville (Congo belge). (On the Proportion of the Three Species of Malarial Parasites among the Native Babies of the "Consultation des Nourrissons" of Stanleyville (Belgian Congo).)—*Riv. di Malariologia.* 1933. Sept.–Oct. Vol. 12. No. 5. pp. 888–896. English summary p. 1064.

SWEET (W. C.); RAO (B. A.). Notes on Malaria in Mysore State. Part I. The Topography, Meteorology and Malarial Seasons of Mysore [SWEET].—*Records of the Malaria Survey of India.* 1933. Dec. Vol. 3. No. 4. pp. 635–661. Part II. The Anophelines of Mysore State [SWEET].—*Ibid.* pp. 663–674. Part III. Spleen and Parasite Rate Relationships [SWEET].—*Ibid.* pp. 675–687. Part IV. Experimental Control of Malaria with Paris Green and Plasmoquine [SWEET & RAO].—*Ibid.* pp. 689–718. With 4 graphs.

TOULLEC & MOREAU. Essais de traitement par l'*atébrine* sur des cas de paludisme quinino-résistant de la Haute-Région tonkinoise.—*Bull. Soc. Méd.-Chirurg. Indochine.* 1933. Sept. Vol. 11. No. 6. pp. 723–736.

TUNISIE MÉDICALE. 1933. Sept.–Oct. Vol. 27. No. 8. pp. 309–372. With 6 figs. on 3 plates.—Numéro consacré au paludisme (1er partie). [4 papers.]

BERIBERI AND EPIDEMIC DROPSY.

ANDRÉ (L.). L'étiologie du béribéri (à propos de quelques cas observés en Chine). [**Etiology of Beriberi.**]—*Arch. Méd. et Pharm. Nav.* 1933. July–Aug.–Sept. Vol. 123. No. 3. pp. 508–532. [33 refs.]

Conclusions are drawn concerning the etiology of beriberi from a study of cases seen in China.

After reviewing in detail the whole subject of beriberi etiology the author draws the following conclusions :—The disease is not a pure avitaminosis and a study of acute cases, as seen for example in an outbreak at Hankow in 1929, shows clearly that it has the characteristics of an infectious malady. BERNARD's B. Asthenogenes is responsible for the toxi-infection character of beriberi. This organism acts more powerfully when the resistance of the patient is lowered as, for example, by a diet deficient in vitamin B. Three etiological factors are present, viz., the infecting organism, a faulty gastro-intestinal condition associated with carbohydrate fermentation and a lowered resistance.

As a result of these views the following measures are suggested :—Patients should be isolated and subjected to an antiseptic regime of the gastro-intestinal tract. Care should be taken that decorticated rice is not given in large quantity and, if need be, it should be suppressed altogether. Food rich in vitamin B, or better still vitamin preparations as issued in the Dutch East Indies, should be given.

A. D. Bigland.

YANG (Chi-Shin) & HUANG (K. K.). **Beriberi in Nanking.**—*Chinese Med. Jl.* 1934. Jan. Vol. 48. No. 1. pp. 20–36. [29 refs.]

A review of beriberi based upon 109 cases in Nanking.

Among the conclusions the following points may be mentioned :—Over 64 per cent. of the cases were in the age group 20–29. 43 per cent. of cases followed a febrile illness, usually malaria. The highest incidence of the disease was in July, August and September, coinciding with the seasonal incidence of malaria. It was found that the oedema of beriberi is not associated with lowering of the serum proteins. Two instances of cerebral oedema were recorded and transient hypertension is thought to be due to an increase of intracranial tension. The etiological importance of excessive muscular work in persons living on a deficient diet is stressed and the use of mercurial diuretics (salyrgan and novasurol) in the treatment of oedema is recommended.

A. D. B.

CRUZ (Alberto). Beri-beri—alguns dados, principalmente epidemiologicos, no surto da cidade de Campos—1932–1933. [**Epidemiological Factors in the Outbreak of Beriberi in Campos (Rio de Janeiro), 1932–1933.**]—*Arch. Brasileiros de Med.* 1933. Dec. Vol. 23. No. 12. pp. 325–347.

The first cases made their appearance in November 1932 and in about 7 months there were 434 known cases. Of this total 211 were recorded in the town, Campos, itself, 189 in the rural zone, 32 in other municipalities. It is highly probable that the total exceeded five hundred. Of the 211 in the town 192 lived on the right bank of the

River Parahyba and only 19 on the left bank. Tables are presented to show the distribution by race (colour), age and sex. Of the 434 there were 236 white, 125 mulatto and 64 black (9 not mentioned); 307 were males and 127 females; most (252) were between 20 and 40 years of age, the same number, 126, in each of these decades. Unless any of the 6 whose ages are not stated were under 10 years, there were none below this age. There were 16 fatal cases, 8 in the town among 211 (3·9 per cent.), 4 in the rural districts (2·1 per cent.), 4 others occurred in the hospital for beriberi. A list is given of the various articles of food in use and their nutritive value as estimated by CHICK, HUME and COOPER some 20 years ago. The remainder of the article is taken up by rather desultory discussion. *H. H. S.*

TÓMASSON (Helgi). **Beri-Beri in Iceland.**—Reprinted from *Acta Psychiat. et Neurol.* 1933. Vol. 8. No. 1–2. pp. 31–35.

An account is given of a small epidemic of beriberi occurring in the Westman Isles, Iceland.

Sixteen cases of beriberi were observed during the fishing season (beginning of January–middle of May). The clinical appearances were typical and it is interesting to note that the calf muscles were often swollen and tender as a result of intracellular water-retention (see abstract of paper by GOIRAN in this issue). The usual cardio-vascular signs were noted and Aalsmeer's adrenaline test gave strongly positive results. Treatment with yeast was successful.

The diet of the Icelanders has undergone considerable alteration during recent years. No longer is milk an important part of the food and the old rye-cakes have been largely replaced by white bread. Of the cereals, polished rice and oatmeal, both poor in vitamin B_1, are mostly taken and potatoes are the only vegetable in general use. Fish is a constant food, but fresh meat is only eaten occasionally by the poorer classes. Conditions in these islands correspond with those found in Newfoundland and it is agreed that fresh fish, even in relatively large quantities, is an insufficient source of Vitamin B_1. *A. D. B.*

KOLKA (P. V. G.). Beriberi í Vestmannaeyjum. Brádabirgdarskýrsla. [**Beriberi in Westman Islands.**]—Reprinted from *Laeknabladid.* 1933. 6.–8. tbl. 18 pp. [25 refs.] English summary.

Four cases of anaesthetic polyneuritis of the lower extremities with cardiac symptoms are described. The patients were all fishermen in an Icelandic fishing village. Their diet was definitely deficient in Vitamin B. The disease was cured in a very short time by the use of yeast and diet improvement. It is concluded, therefore, that the condition was beriberi. *A. D. B.*

ELSHOUT (J. M.) & LENTJES (L. J. M.). De beri-beri epidemie op het eiland Onrust. [**Epidemic Beriberi on the Island of Onrust.**]—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1933. Oct. 10. Vol. 73. No. 21. pp. 1288–1298.

An epidemic among naval prisoners on an island off Holland.

A number of European and native sailors were placed as prisoners on the island of Onrust, at the mouth of the Zuider Zee on 12th February. On 19th March the first two cases of beriberi were diagnosed. By 12th April the number of cases had risen to a maximum of

56. The type of the disease was mild and symptoms complained of were weakness in the bones, paraesthesiae, cramps in the calf muscles and difficulty in walking. A stamping gait with stiff legs, the heel first to the ground and knee in slightly recurved position was the common gait. Only one patient showed a typical cock walk. Slight oedema was present over the tibia; achilles and patellar reflexes disappeared. Shortness of breath and palpitation were scarcely complained of. In fact cardiac symptoms were slight—some enlargement of the right heart, a quick reacting pulse, a normal blood pressure, and in some cases a vascular murmur especially over the crural artery. The therapeutic measures taken were, the allowance of a more varied diet (Katjang idjoe, more fresh vegetables, etc.), amelioration of the rigorous imprisonment, more exercise, gymnastics, more fresh air and games. It is natural to look to the feeding as the cause of this epidemic, but the authors dismiss this suggestion as untenable. The food, in so far as it involved a change of previous diet, was merely one from a more liberal to a more frugal one and from white rice to the silver-husk rice of the Army Service Corps. Other factors must be sought whose combined action was sufficient to precipitate beriberi, in spite of the protection of otherwise good food. The factors which are suggested are the imprisonment, insufficiency of exercise, confinement and psychic depression. The question, however, is raised whether the diet in the Dutch navy generally is sufficiently prophylactic against beriberi in times of stress. *W. F. Harvey.*

West (Augustus P.) & Cruz (Aurelio O.). **Philippine Rice-Mill Products with Particular Reference to the Nutritive Value and Preservation of Rice Bran.**—*Philippine Jl. Sci.* 1933. Sept. Vol. 52. No. 1. pp. 1–78. With 1 fig. & 10 plates. [70 refs.] [Summary appears also in *Bulletin of Hygiene.*]

The average yearly production of paddy (unhulled) rice in the Philippines is two million metric tons. In the Philippine process of milling the rice is passed through a huller, the hulls are used in the boiler, and the rice is polished, in which process the bran, consisting of the entire seed coat and the embryo as well as most of the aleurone layer is removed. Polished rice usually contains remnants of the oily aleurone layer, and the oil tends to become rancid when the rice is stored for some time. Rice starch is used in laundering, preparing foods, making pastes, medicinal tablets and cosmetics. Rice hulls are used for fuel, packing hygroscopic materials, filtering, and the ash makes good polishing powders. Polished rice keeps much better than, and does not become infested with insects as does unpolished rice. The fats, proteins and vitamins of the paddy rice are contained chiefly in the bran. High-grade, moisture-free bran should contain at least 20 per cent. of vegetable oil. For human consumption the bran should contain practically no hulls as they irritate the intestine, and in milling a very efficient blower should be used. The presence of hulls in the bran can be determined microscopically.

The proteins of rice-bran are similar to those of meat and milk and soy-bean; their biological value compares favourably with those of meat. The bran contains an excess of phosphorus as compared with lime and in this respect is unbalanced. In other respects it is an excellent food, being more nutritious than hydraulic copra cake, wheat bran, Graham and straight grade flour. If its natural flavour is

objected to, this may be toned down by mixing with wheat flour; 3 parts of wheat flour and 1 of bran make a good mixture for bread and cakes. The bran does not contain gluten and the wheat flour remedies this deficiency. Beriberi is a very common disease among the poor of the Philippines and for this reason the vitamin B_1 content of the bran assumes special importance. The yield of tikitiki extract from bran varies considerably; the potency of 1 cc. of the standard extract is that of 14·5 gm. of high-grade rice bran. It has been estimated that for people who are susceptible to beriberi 30 gm. of rice bran daily provides sufficient vitamin B_1. The annual production of rice bran in the Philippines is about sufficient for all the people requiring it for its medicinal value and for others who might possibly benefit from its use.

Deterioration of rice bran is caused by insect infestation, and also by hydrolysis of the rice oil in the presence of moisture, due to the lipases present in the vegetable tissue. This decomposition causes a disagreeable taste. The authors' results indicate that the best method for preserving the bran is to heat it at a temperature of about 105°C. for 3 hours and then keep it in moisture-proof packages, for which cellophane is the best material. The vitamin content is not affected by this process, and the lipases only appear to be rendered inactive, for if moisture gains access hydrolysis commences. Heating at 120°C. for 6 hours appears to destroy the enzymes. In preparing rice bran for storage a cooker containing a stirrer should be used as stirring assists the removal of moisture; the bran should be packed whilst hot. Where proper facilities are not available, the bran may be heated, with continual stirring, in a frying pan over a low fire until the bran turns slightly darker in colour; it is then placed in a can or glass jar which must be closed tightly. The bran will then keep in good condition for a week or more. The heated bran has a more pleasant flavour than the fresh raw bran. In the Philippines, fine rice bran is very cheap and is used chiefly for feeding cattle and poultry. For the poorer classes, whose diet is principally polished rice, the use of rice bran would remedy to a considerable extent the present deficiencies in fats, proteins and vitamins. It would prevent beriberi and improve the general health, and at the same time develop the natural resources of the country. *H. N. H. Green.*

VAN VEEN (A. G.). Der Einfluss des Waschens und Daempfens auf den Gehalt an vitamin B_1 von Reisproben verschiedenen Schleifgrads. [**B Vitamin Content of Rice of Different Degrees of Polish after Washing and Steaming.**]—*Meded. Dienst d. Volksgezondheid in Nederl.-Indië.* 1933. Vol. 22. No. 3. pp. 181–189. [10 refs.]

The author holds the view that in the Dutch East Indies too much attention is paid to the degree of polishing of rice as indicative of its vitamin content whereas, as a matter of fact, the after-treatment of rice (cooking, steaming, etc.), is of even greater importance in this respect. [For details see page 19, *ante.*] *A. D. B.*

ISWARIAH (V.) & KUTUMBIAH (P.). **Post-Puerperal Polyneuritis.**—*Indian Med. Gaz.* 1934. Jan. Vol. 69. No. 1. pp. 13–16. [13 refs.]

Peripheral neuritis occurring in women during the puerperium is described and the possible association of the condition with beriberi is discussed.

From a full examination of the literature it appears that peripheral neuritis is not a commonly recognised complication either of pregnancy or of the puerperium. 24 cases observed in Vizagapatam, an endemic area of beriberi, showed typical peripheral neuritis with oedema beginning 2–3 months after labour. The women were otherwise apparently healthy and the condition occurred most frequently in primiparae. The infants in about 70 per cent. of the cases were healthy and suckled by the mother. There was only one maternal death in the series.

When compared with male beriberi admissions at the same time the remarkable absence of cardiac symptoms in the women suggested that beriberi was not the cause of the outbreak. Though the strain of childbearing may render an unbalanced diet insufficient, the authors suggest that some endocrine disturbance may be responsible. Nevertheless, the fact that such outbreaks only occur in areas where beriberi is endemic cannot be overlooked. *A. D. B.*

AALSMEER (W. C.). Over de wijze van ontstaan van het vaatsyndroom en de verklaring van het adrenalineeffekt bij beri-beri. [**Mode of Development of the Vascular Syndrome and Explanation of the Adrenalin Effect in Beriberi.**]—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1933. May 23. Vol. 73. No. 11. pp. 659–668. [14 refs.]

Numerous papers have appeared on this subject by AALSMEER and by WENCKEBACH himself (this *Bulletin*, Vol. 25, p. 871; Vol. 26, pp. 352, 517; Vol. 28, p. 460; Vol. 29, pp. 92, 614 and Vol. 30, pp. 159 and 543). The importance of the vascular symptoms in beriberi lies in their hydrodynamic explanation and the suitability of this disease for testing various hypotheses. What is the cause of the rapid, bounding (*celer et altus*), and rippling pulse, the presence of vascular murmurs, the fall of the minimal or diastolic blood pressure and the capillary pulse? These phenomena are not peculiar to beriberi but are manifest also in arteriovenous aneurysm, exophthalmic goitre, aortic insufficiency and severe anaemias. An explanation has been found, especially through the work of BRAMWELL, in the character of the wave front in the aorta —itself dependent on the increased volume of blood expelled by the heart, the decreased expulsion time and the low diastolic pressure— and in the rapidity of peripheral discharge ("leak"). The sum total of the different factors concerned is described under the word "gradient," expressing the fact that the rapidity of development of the fall and an unstable wave front are the most important factors concerned in the vascular syndrome. The gradient becomes an index of the degree of vascular symptoms. Adrenalin effect is attributable to its pharmacological action on the heart and not to its action on the blood vessels. Adrenalin accentuates the syndrome by increasing the steepness of the "gradient." *W. F. Harvey.*

GOIRAN. Altérations musculaires particulières au cours de polynévrites béribériques. [**Muscle Changes Peculiar to Beriberi.**]—*Bull. Soc. Méd.-Chirurg. Indochine.* 1933. Oct. Vol. 11. No. 7. pp. 863–875. With 2 figs.

A description is given of certain muscular changes found in cases of beriberi.

This change is localized, entirely or in part, to the "jumeaux internes" muscles (gastrocnemii) and is characterized by the volume of these muscles being maintained in contrast with the wasting of surrounding muscles. On palpation a peculiar hardness, like that of hard indiarubber, is felt and on pinching or percussion there is a diminution of contractility. The lesion is usually symmetrical and seems to appear about one month after the onset of neuritis. It is not accompanied by appreciable modification of the arterial circulation in the limb. In spite of pathological investigations upon pieces of affected muscle removed during life the exact nature of the lesion remains obscure. Apparently atrophy of muscular fibres, fatty degeneration and round-celled infiltration constitute the chief findings. *A. D. B.*

URMY (Thomas V.), RAGLE (B. Harrison), ALLEN (Arthur W.) & JONES (Chester M.). **Beriberi Secondary to Short-circuited Small Intestine.**—*New England Jl. of Med.* 1934. Feb. 1. Vol. 210. No. 5. pp. 251–254. [12 refs.]

A description is given of a case of beriberi following a short-circuit operation on the small intestine. The condition was probably due to defective vitamin absorption and was cured by disconnecting the intestinal anastomosis.

The association of beriberi with gastro-intestinal lesions is much less common than it is in pellagra. The present case is that of a native lawyer, aged 47, who developed intestinal obstruction following appendectomy. A lateral anastomosis between loops of small intestine was performed and diarrhoea, followed later by vomiting, began. Typical beriberi symptoms appeared during the following 2–3 years (peripheral neuritis, oedema, aphonia and cardiac symptoms which did not respond to digitalis therapy). After two blood transfusions the patient was given brewers' yeast and later, liver extract, cod liver oil, insulin, etc., were added. His condition soon improved considerably. Later, again at operation, a hugely dilated jejunum was found and the entero-enterostomy was disconnected. Following this he steadily improved and 2½ years after the last operation he had completely recovered except for slight weakness of the voice and some uncertainty in walking. It may be mentioned that renal calculi developed during the time that the small intestine was short circuited, possibly owing to defective absorption of vitamin A.

Two other cases, similar to the above, are mentioned. In one beriberi developed in a patient with ulcerative colitis and ileostomy; and in the other neurological symptoms of beriberi appeared 2½ years after an enterostomy between the stomach and lower ileum. Both these cases were greatly improved by suitable therapy. *A. D. B.*

MASSIAS (Charles). Le traitement du béribéri par une préparation contenant vitamine B et acides aminés (vitaminol). [**Treatment of Beriberi by Vitamin B or Amino Acids.**]—*Bull. Soc. Méd.-Chirurg. Indochine.* 1933. June. Vol. 11. No. 4. pp. 386–391. [14 refs.]

Since 1930 the author has treated beriberi cases in Cochin China with tablets containing vitamin B and various amino acids. The results have been very satisfactory.

Each tablet contains 12 rat units of vitamin B combined with the following amino acids:—leucine, cystine, lysine, histidine, arginine and polypeptides. The dose is 4 tablets a day taken with meals of rice, "potage de riz," fish and Nuoc-mam. Since 1933 the same mixture has been given in the form of a paste flavoured to suit the native taste. This preparation contains also tryptophane and a substance in the casein amino acid group which has marked growth-stimulating properties. The dose of this paste is one "cuiller à soupe" a day (the dose may be doubled or trebled) dissolved in water or mixed with rice, fish and vegetables. The treatment has the great advantage of cheapness. The results obtained are as follows:—in 1930, before the treatment was begun, out of 275 beriberi cases 25 died (9·09 per cent.). In 1931, after treatment, out of 322 cases there were 23 deaths (7·14 per cent.), and in 1932 out of 274 cases there were only 8 deaths (2·09 per cent.). Moreover, the fatal cases were moribund on arrival at hospital.

A. D. B.

CHOPRA (R. N.) & BOSE (S. C.). **Cardiovascular and Other Manifestations of Epidemic Dropsy.**—*Indian Med. Gaz.* 1933. Nov. Vol. 68. No. 11. pp. 605–617.

This paper gives a very detailed account of the cardiovascular manifestations met with in epidemic dropsy. The disease in nearly every case is associated with the ingestion of contaminated rice grain. A bacillus, similar to that described by BERNARD, was commonly found in the grain and was recovered from the urine and stools in many cases. Toxins elaborated by this organism resemble histamine in having a marked effect upon the capillaries. For cardiac failure in this condition digitalis is useless but tincture of ephedra gives good results.

Cardiac involvement is the rule in epidemic dropsy but its severity varies. It is often more marked in patients with constipation, and when diarrhoea is prominent cardio-vascular symptoms are often slight. Dyspnoea is an early feature and oedema occurs more or less in all cases. The initial oedema is of the solid type and the skin is dusky-red, hot and tender but as cardiac failure sets in the dropsy presents the usual features of that state. Anaemia is a prominent feature. The systolic blood pressure is low (rarely above 110 mm.) while the diastolic reading is 50 mm., or less.

In epidemic dropsy the myocardium shows neither inflammation, degeneration nor hypertrophy. The only constant change is capillary dilatation. Cardiac failure, when it occurs, is of the congestive type. Three forms are recognizable:—(1) *Acute.*—Cardiac failure is present at the beginning and rapidly progresses so that death may occur in 4–7 days. The clinical picture is that of an acute left heart failure. (2) *Subacute or chronic.*—These cases present combined right and left heart failure with slight cyanosis, jugular distension and general venous congestion. Recovery is the rule. (3) *Formes Frustes.*—In these the heart escapes or is only very slightly affected.

Clinically the heart is enlarged and though bruits are heard the valves are normal. Tachycardia is constant (110–130) and out of proportion to the pyrexia. The pulse is sometimes of the Corrigan type. On venesection the blood is of a peculiar dark chocolate colour and clots almost at once, the serum being bile-tinted. Fever is an initial and fairly constant symptom and its degree is a rough measure

of the severity of the attack. The authors state that there is undoubted evidence of peripheral neuritis in epidemic dropsy.

Treatment consists firstly in removing rice entirely from the diet Progress is much slower if this is not done and relapses occur when the patient disobeys orders and resumes his rice diet. For severe diarrhoea liq. ferri perchloridi (15–30 minims) is helpful. Digitalis and the other members of the group were found to be useless in cardiac failure. Having regard to the capillary dilatation any drug which will constrict these vessels and restore their tone should prove beneficial. Therefore adrenaline (daily intramuscular injections of 2–4 minims) was tried and relief followed. Unfortunately, however, after a few days sensitiveness to the drug developed and it had to be discontinued. Good results were obtained with tincture of ephedra (20–30 minims, 2 or 3 times a day with or without iron and strychnine). When diarrhoea is present the drain of fluid from the body may be to some extent relieved by combining calcium lactate (10 grains 2–3 times a day) with the above treatment. *A. D. B.*

DE ARAUJO (Eduardo). Sobre a etiologia e diagnostico do beri-beri.—*Arch. Brasileiros de Med.* 1933. Dec. Vol. 23. No. 12. pp. 382–409.

AUSTREGESILO (A.). Neuro-mieloses beribericas.—*Arch. Brasileiros de Med.* 1933. Dec. Vol. 23. No. 12. pp. 357–368. [25 refs.]

FILHO (Miguel Couto). Beriberi de causa infecciosa.—*Brasil-Medico.* 1933. Dec. 9. Vol. 47. No. 49. pp. 869–870.

GAUDUCHEAU (A.). Le riz dans l'hygiène alimentaire de l'Extrême-Orient.—*Bull. Soc. Path. Exot.* 1933. May 10. Vol. 26. No. 5. pp. 677–687. [Refs. in footnotes.]

DE MENDONÇA (João I.). Beri-beri (lesões da valvula tricuspide).—*Arch. Brasileiros de Med.* 1933. Dec. Vol. 23. No. 12. pp. 348–356.

TAVARES (Armando Sampaio). O systema vegetativo no beriberi.—*Arch. Brasileiros de Med.* 1933. Dec. Vol. 23. No. 12. pp. 369–381. [29 refs.]

TOULLEC & GOIRAN. A propos d'un cas de béribéri cardiaque d'emblée chez un Européen.—*Bull. Soc. Med.-Chirurg. Indochine.* 1933. Nov.–Dec. Vol. 11. No. 8. pp. 977–982.

VILLELA (Gilberto V.). Protéines du plasma, calcium et cholestérol dans le béribéri.—*C. R. Soc. Biol.* 1933. Vol. 113. No. 27. pp. 1277–1279.

PELLAGRA.

AYKROYD (W. R.). **Pellagra.**—*Nutrition Abstracts & Reviews.* 1933. Oct. Vol. 3. No. 2. pp. 337–344. [30 refs.]

A review of the subject containing some interesting public health statistics.

Much of the review is founded upon papers summarized from time time in this *Bulletin.* The section dealing with pellagra as a Public Health problem contains some interesting statistics. In the U.S.A. the total number of deaths from pellagra in 1924 was 2,006 (2·5 per 100,000). The figure then steadily increased so that in 1928 the death rate per 100,000 was 6·4. In the following two years there was a slight decrease. In Italy a very different state of affairs is recorded. In the period 1896–1900 the death rate per 100,000 was 10·7. Since then the rate has steadily declined, until in 1928 it was only 0·2 (total deaths 85 as compared with 3,426 in 1896–1900). A law passed in 1902 prohibited the sale of spoiled maize and compelled the provision of public maize desiccators. Rural bakeries were set up for the supply of cheap wheat bread and charitable kitchens were established which provided soup, and sometimes bread and meat, free or at very low prices. Furthermore, special pellagra hospitals were founded together with asylums for the care of the children of pellagrins. " It is impossible to say how far the diminution of pellagra in Italy can be ascribed to legislative measures, and how far to changes in the diet of the people brought about by rising standards of living and other causes."

In Rumania, according to figures supplied by the Ministry of Health of Bucharest, the total number of pellagra cases in 1930 was 48,542 with 1,717 deaths (death rate of 9·5 per 100,000). In 1932 there were 55,013 cases with 1,656 deaths (death rate 9·0). It is pointed out that these Rumanian statistics are considerably understated. In the U.S.A. it has been found that the increase in the pellagra mortality rate is smaller than the increase in morbidity. This suggests that the curative effect of certain foods enables more sufferers to survive.

A. D. Bigland.

STANNUS (Hugh S.) & GIBSON (Charles R.). **Pellagra in Great Britain.** —Reprinted from *Quarterly Jl. Med.* 1934. Apr. N.S. Vol. 3. No. 10. pp. 211–236. With 1 plate. [39 refs.]

This paper describes in detail a case of pellagra in a child observed in Britain. The account is perhaps unique in presenting a full history of the onset, course, recovery and subsequent progress. There is also a summary of all the pellagra cases published in this country.

Pellagra is a rare disease in Great Britain. The first death from this cause was officially recorded in 1912, though the first clinical description dates from 1866, or possibly 1865. The patient here described is a female, an only child of respectable working class parents living in Weymouth. In April 1927 (at the age of 3 years 8 months) the first symptom was noted, viz., severe " sunburn " involving the neck, hands and the exposed parts of the legs. In August of that year the child became " nervous " and suffered from diarrhoea with abdominal pain. By September the dermatitis had disappeared. Beginning at Easter 1928 an attack similar to the above was recorded with complete recovery in the following winter except for a roughness of the skin of

the hands. During the following years the same sequence of events took place with diarrhoea, change of character, vertigo and unsteady gait. In May 1931 (when the child was nearly 7 years old) a tentative diagnosis of pellagra was made and this was confirmed in June of that year.

"The average daily diet during the years 1928–1930 was as follows: early morning, a cup of tea and a biscuit; breakfast, a rasher of bacon and a tomato or a boiled egg, a glass of water; mid-morning at school, a slice of bread and butter, a glass of milk; mid-day dinner, two potatoes, peas, gravy, sometimes fish like mackerel, or chicken (she did not care much for fish and seldom would eat meat), a little milk pudding or stewed fruit; before tea, a slice of bread and butter; at tea-time an egg (she was very fond of eggs), two pieces of bread and butter with jam, sometimes tinned salmon, a glass of water or a cup of tea (she liked tin salmon and bread and butter); supper, a bowl of bread and milk or sometimes boiled onions and bread and butter, occasionally fish and chips. She had always had a certain amount of fruit—apples, bananas, and strawberries, but disliked oranges and other fruit. During 1931 the child was very difficult to feed and took little except three eggs a day, some milk, and bread and butter. The child had had pop-corn occasionally when quite young."

When seen at the French Hospital, London, the child presented the following appearances: a typical dermatitis (a good photograph confirms this), gastro-intestinal disturbances, signs of nervous system involvement and irregular pyrexia. At the angles of the mouth and at the external canthus of each eye the muco-cutaneous junctions showed a heaped-up sodden white condition of the epithelium and on unexposed areas of skin there was a definite roughness (gooseskin). The tongue was not affected. Various laboratory investigations were carried out but no definite abnormality was found. Shortly after admission to hospital the child became very ill and her condition was one of a semi-typhoid state. The stool at this time showed the presence of a small amount of porphyrin (probably of vegetable origin) but the blood and urine were negative for haematoporphyrin. The skin showed no photo-sensitivity. Rapid improvement followed the taking of one tablespoonful of dry fresh brewers' yeast twice daily (liver extract was tried but discontinued after a few days). On July 17th, 1931 the child was allowed to return home. The mother was instructed about the importance of a well-balanced diet and the yeast treatment was continued. In the summer following discharge from hospital there was a very slight relapse but when seen again in June 1933 the child was in excellent health and only exhibited some goose-skin roughness and very slight unsteadiness when turning round quickly.

The second part of the paper presents a detailed analysis of all pellagra cases published in this country (some 78 cases). It will be noticed that there is a greater incidence of pellagra in the female sex and that it has an association with mental disease. The Registrar-General's reports show that the total number of deaths due to pellagra during 1912–1931 was 131 (20 males and 111 females). *A. D. B.*

Egypt. Ministry of the Interior. Department of Public Health. Lunacy Division Report for the Year 1932 including the Mental Hospitals of Abbassiya and Khanka, and Khanka Criminal Asylum.—[**Pellagra** p. 3.]

"Pellagra is well known to be a very common disease in Egypt and several hundreds are admitted annually into the Mental Hospitals. Our experience extends over thirty years and it is impossible not to

have formed in that time various definite opinions about this disease. One, undoubtedly, is that the majority of pellagrins apparently recover under treatment but are liable to show definite pellagrous symptoms whenever their health runs down from some intercurrent disease and this is especially marked during a fatal illness and in spite of the fact that the diet in the Hospitals is a sufficiency diet; also cases which undoubtedly never had pellagra do not show these symptoms under similar conditions. The opinion of the medical staff in the Mental Hospitals is that pellagra can usually be kept in abeyance by a sufficiency of food and treatment for symptoms but it is extremely doubtful whether it can ever be eradicated and it is liable to flare up at the above stated period.

"The pellagrin patients come invariably from districts where maize is a staple form of food for at least several months in the year. They do not come from the towns nor from Middle and Upper Egypt where millet replaces maize but they are present in Upper Egypt in districts where maize is largely cultivated such as Komombo. The diet in Upper Egypt is probably poorer than in Lower Egypt and the sun is so much stronger that one would expect more cases from Upper than from Lower Egypt if pellagra was a pure deficiency diet disease and the sun a powerful factor. Also the nervous system is so definitely deranged in pellagra as exemplified by the alteration of the reflexes even such gross examples as ankle clonus being common; the reflexes do not become normal under treatment although all other symptoms may be eradicated. In fact it is impossible to conform our ideas, in the light of our experiences, to the theory that pellagra is a pure diet deficiency disease, and we are strongly of the opinion that there is something more and that it is connected with maize, though a deficiency diet allows the disease to demonstrate its manifestations.

"Most of the pellagrins are admitted in March, April and May when the weather is comparatively cool." *A. G. B.*

WYJASNOWSKY (A. J.). Zur Frage der Pellagra. [**What is Pellagra?**]—*Arch. f. Schiffs. u. Trop.-Hyg.* 1934. Jan. Vol. 38. No. 1. pp. 31–37.

Is pellagra a disease *sui generis* or is it a symptom-complex?

Observation on more than twenty cases of pellagra were made at the psychiatrical hospital in Tashkent. More than half of the patients died and most of those that were discharged had an obviously bad prognosis. Three had intestinal infestations; one with Lamblia, another with *Trichomonas intestinalis*, and a third with *Entamoeba histolytica*. In another group of cases it was found that out of 14 autopsies on pellagra cases 3 men and 1 woman had carcinoma of the alimentary tract. From these observations the author concludes that pellagra is a symptom-complex.

[The association between pellagra and carcinoma of the alimentary tract seems to be generally admitted but the presence of intestinal parasites may be only a coincidence.] *A. D. B.*

STANNUS (Hugh S.). **A Nutritional Disease of Childhood associated with a Maize Diet—and Pellagra.**—*Arch. Dis. in Childhood.* 1934. Apr. Vol. 9. No. 50. pp. 115–118.

In a recent issue of the *Archives of Disease in Childhood* Dr. WILLIAMS described a syndrome occurring in native children in the Gold Coast

Colony [*ante*, p. 344]. The children's diet was faulty and contained excess of white maize. The author of the present paper gives reasons for his opinion that the syndrome is in reality pellagra.

The age of the children was 1–4 years. The onset of the condition was associated with irritability, loss of normal colour and glossiness of the skin and hair, attacks of diarrhoea and slight oedema of the hands, feet and face. Suddenly, after 7–10 days black patches appear on the extensor surfaces of the ankles, knees, wrists and elbows. This skin condition spreads and covers the legs and forearms with a "crazy pavement of thickened epidermis." Exfoliation takes place leaving pink areas underneath and small patches of desquamation are also seen on the face, back and elsewhere. Sores on the mucous membranes of the mouth are described. As the disease progresses diarrhoea becomes constant and death ensues, in untreated cases, in a month or less.

The author argues that the skin manifestations described are exactly those met with in pellagra as seen in dark-skinned races. It is pointed out that the distribution of pellagra dermatitis is variable and though it is usually found on exposed areas any form of physical irritation may act as an exciting factor and thus cause the rash to appear on unusual sites. Small sodden areas of white skin round the mouth, external canthus of the eye, prepuce, vulva and anus are also typical. For treatment it is suggested that yeast should be tried and that a search should be made for some naturally occurring fermentable juice similar to the "toddy" found so efficacious by BRAY in the treatment of infantile beriberi in the Central Pacific Island of Nauru.

A. D. B.

CUMMINS (Robert C.). **Observations on Pellagra—with Report of a Case.**—*Irish Jl. Med. Sci.* 1934. Mar. 6th Ser. No. 99. pp. 113–120. With 2 figs. on 1 plate.

A case of pellagra in the neighbourhood of Cork is here reported.

The patient, a man aged 42, had attacks of summer gastro-enteritis for some years. These became more severe and latterly were accompanied by darkening of the skin and sores round the mouth. Photographs show the presence of a fairly typical pellagrous dermatitis and the clinical appearances, including mental changes, were more or less characteristic. The man's diet had consisted of bread, butter, eggs, meat, potatoes and cabbage. He was not, however, fond of meat but took much porridge made from maize meal. A visit to the man's home, a small farmhouse in the country, revealed the fact that the other members of the family were healthy. They disliked the maize meal and the children refused to eat it. Apparently a vitamin B_2 deficiency, probably periodic, together with the consumption of maize was the cause of the disease. The patient's physical condition improved somewhat on a diet rich in animal protein with the addition of yeast.

A. D. B.

SPIES (Tom D.). **Skin Lesions of Pellagra: an Experimental Study.**—*Arch. Intern. Med.* 1933. Dec. Vol. 52. No. 6. pp. 945–947.

Evidence is presented showing that pellagra dermatitis often improves while the patient is restricted to a diet of corn-starch and lactose.

The author summarizes his work as follows:—"(1) It has been shown in this experiment that persons with pellagra tolerating a diet of

lactose and corn-starch show improvement of their cutaneous lesions. This work confirms and somewhat extends my previous observation that the dermatitis of pellagra improves while the patients receive a so-called 'pellagra-producing' diet. (2) It is recommended that improvement in dermatitis be interpreted with great care before accepting it either as an index of efficacious treatment or of favorable prognosis. (3) It appears possible that the specific chemical substance related to the development of the dermatitis is not the same as that affecting manifestations of the disease in the gastro-intestinal or central nervous system." *A. D. B.*

MONAUNI (Josef). Ueber Pellagra in der Steiermark. [**Pellagra in Styria.**]—*Wien. Klin. Woch.* 1933. Nov. 27. Vol. 46. No. 47. pp. 1413–1418. [61 refs.]

A detailed description of two fatal pellagra cases which occurred sporadically in Styria.

The first case was a male in a good social position. Alcohol was the probable cause. The second case was that of a male labourer. The history extended over 4 years and he had lived upon a maize diet. There was a possibility that here, too, alcohol played a part, though some constitutional defect may have been present as a brother in America also suffered from pellagra.

Two further cases of pellagra associated with carcinoma of the stomach are described. *A. D. B.*

HØFMAN-BANG (A.). Syv tilfaelde af secundaer pellagra. [**Seven Cases of Secondary Pellagra.**]—*Hospitalstidende.* 1933. Nov. 2. Vol. 76. No. 44. pp. 1088–1095. With 5 figs.

Only 12 cases of secondary pellagra have hitherto been recorded in Denmark. But as it has been suggested that other cases are to be found merely for the looking, particularly in institutions for the insane, Hofman-Bang has scrutinized not only the present inmates of the asylum to which he is attached, but also the records of patients discharged since this asylum was opened in 1915. The result of these investigations is a crop of new cases, all of which conform to the now fairly well defined clinical picture of secondary pellagra.

In every case the skin changes were characteristic. Another feature common to all was some form or other of chronic, gastro-intestinal disturbance which had presumably interfered with the absorption, in adequate quantities, of the vitamin associated with this disease. In some cases the administration of spinatin was followed by the disappearance of the skin lesions, but it had little or no effect on the patients' mental condition. Indeed, in no case did there seem to be any direct causal relationship between the various psychoses on the one hand and the secondary pellagra on the other. *C. Lillingston.*

JENSEN (Ellen Vibeke). Tre tilfaelde af secundaer pellagra. [**Three Cases of Secondary Pellagra.**]—*Hospitalstidende.* 1934. Mar. 13. Vol. 77. No. 11. pp. 319–322.

Since Hess THAYSEN in the spring of 1933 drew attention to the existence of secondary pellagra in Denmark, search has been made for this disease in many quarters, and a score of cases have been found and published. Ellen Vibeke Jensen adds three more to this number, her patients, as in the case of her predecessors, being asylum inmates.

After giving details of each case, she notes that a scrutiny of the records of the past 10 years of patients in her asylum who died there or were discharged has failed to reveal any case which could definitely be labelled pellagra; for though there were some cases of protracted diarrhoea refractory to treatment, there was no record of the characteristic skin lesions. All her three patients were physically very debilitated when the signs of pellagra appeared, and the mental disease from which they suffered was severe and had lasted a long time. In two the gastro-intestinal disease took the form of obstinate diarrhoea, and in the third case incessant vomiting was accompanied from time to time by diarrhoea. In all three cases, these gastro-intestinal phenomena preceded the appearance of pellagra. Two of the patients had been artifically fed, their food consisting of fresh milk, albumin-maltose, sugar, eggs, and the juice of a lemon or tomato. This dietary should have supplied the necessary vitamins, and the outbreak of the pellagra may have been determined by the anorexia and inadequate feeding which preceded the artificial feeding. The author also discusses the theory that a severe psychosis may affect the functions of the body in such a way that the digestive system is upset and rendered incapable of adequate vitamin absorption. In this connexion it may be noted that severe psychoses are not infrequently associated with protracted diarrhoea which is refractory to treatment and which seems to have neither a bacterial nor dietetic origin. *C. Lillingston.*

BIGGAM (A. G.) & GHALIOUNGUI (Paul). **Pellagra: its Clinical Features and Pathology with Observations on the Treatment of its Nervous Manifestations by Massive Doses of Iron.**—*Lancet.* 1933. Nov. 25. pp. 1198–1203. [13 refs.]

Massive doses of iron give satisfactory results in the treatment of the nervous manifestations of pellagra.

Twenty-six typical cases of pellagra in Egypt were studied. Parasitic infestation of the bowel was found in 94 per cent., a high figure when compared with the general infestation rate of the Egyptian rural population. This may account for the fact that only one member of a family suffers from pellagra though all the members live under the same conditions. Achlorhydria was present in about half of the cases and none of these showed any secretion of acid after histamine injection. There was apparently no relationship between the condition of the gastric juice and the degree of nervous involvement.

Six cases showing neurological changes were treated with massive doses of iron after the method employed by SARGANT in subacute combined degeneration of the cord. Blaud's pills, in doses of 150 grains daily, were administered for a period of 6–8 weeks. The results were satisfactory, though one patient died a few weeks later from bacillary dysentery. The authors conclude that the administration of iron together with a well-balanced diet is of extreme importance in the treatment of pellagra cases showing involvement of the nervous system.

A. D. B.

LANE (Clayton); STANNUS (Hugh S.). **Helminths and Pellagra.** [Correspondence.]—*Lancet.* 1933. Dec. 9 & 16. pp. 1345; 1395.

In reference to the paper by BIGGAM and GHALIOUNGUI Colonel Clayton LANE draws attention to a letter by H. M. WOODCOCK (1920)

[this *Bulletin*, Vol. 17, p. 148] in which he suggested that in addition to deficient nutrition the presence of a helminthic infection might be necessary for the production of pellagra. Dr. Stannus suggests that the helminth infection plays its part by causing the deficient nutrition.

A. G. B.

RUFFIN (Julian M.) & SMITH (David T.). **The Treatment of Pellagra with Certain Preparations of Liver.**—*Amer. Jl. Med. Sci.* 1934. Apr. Vol. 187. No. 4. pp. 512–521. With 3 figs. & 2 charts.

Liver extracts, when administered orally, give satisfactory results in the treatment of active pellagra. Little or no improvement follows intramuscular injections.

A standard basic diet, containing adequate amounts of proteins, fats, carbohydrates, mineral salts and all known vitamins except vitamin G, was prepared. Pellagra cases showed no improvement on this diet and 3 out of 4 dogs partaking of it died of black tongue in 25–45 days. Ten active pellagrins subsisting on this basic diet were given 90 cc. of an aqueous liver extract daily by the oral route and all showed a satisfactory remission of symptoms. Five cases similarly fed were given intramuscular injections (5 cc. daily) of Liver Extract no. 343. None of these showed any remission, but when the oral administration of the aqueous extract was substituted a dramatic improvement began within 3–5 days and continued until the patients were apparently well.

The effect of sunlight upon the skin was also studied. It was found that " exposure to direct sunlight in North Carolina in the spring and summer months produces dermatitis in active and potentially active pellagrins, but not in normal controls or in pellagrins who have received adequate treatment."

A. D. B.

SPIES (Tom D.). **Treatment of Pellagra by Means of Parenteral Liver Extract.**—*Proc. Soc. Experim. Bioi. & Med.* 1933. Dec. Vol. 31. No. 3. pp. 363–364.

After references to the work of BOGGS and PADGETT and of RAMSDELL and MAGNESS [this *Bulletin*, Vol. 30, pp. 146 and 549] on the administration of liver extract in pellagra the author briefly describes a trial of intravenous and intramuscular liver extract in pellagrins with such severe oral lesions that they refused to eat.

Six patients in whom stomatitis and glossitis were severe received the liver extract intravenously and four others intramuscularly. Within 24 hours the lesions were improved and 72 hours after either form of injection they were healed.

A. G. B.

SMITH (James H.). **The Treatment of Pellagra.**—*Southern Med. Jl.* 1934. Feb. Vol. 27. No. 2. pp. 163–165.

As a result of its use in a case of pellagra with extensive ulceration in the mouth the author suggests that intravenous injections of sodium thiosulphate are of value in this disease. He refers to the reduction of cystine in the finger-nails of pellagrins with widespread dermatitis, demonstrated by PAYNE and PERLZWEIG [see below] as a reason for believing that errors of sulphur metabolism are important in pellagra.

A. G. B.

PAYNE (Sheldon A.) & PERLZWEIG (William A.). **Cystine Content of Finger Nails in Pellagra.**—*Jl. Clin. Investigation.* 1933. Sept. Vol. 12. No. 5. pp. 899–908. With 1 fig. [27 refs.]

The cystine content of the finger nails, and presumably of the skin also, in cases with extensive pellagrous dermatitis is markedly decreased. This reduction is not found in pellagrins without dermatitis.

Reference to the literature shows that sulphur metabolism in pellagra is disturbed. An increased excretion of urinary ethereal sulphates and a reduction of sulphur in the central nervous system of pellagrins have been recorded. Also the amount of cystine in the hair of rats decreases when the animals are fed upon a diet deficient in vitamin G. The high concentration of cystine in the epidermal tissues of the higher animals suggests a possible protective function, and it was hoped that experimental evidence could be obtained indicating that the skin lesions of pellagra are photogenic. It was found that finger nails gave more uniform data from which to judge the cystine content of epithelial tissue. Observations were made upon 36 normal subjects, 40 pellagrins and upon 25 cases of syphilis and tuberculosis. "In 14 cases of pellagra with extensive dermatitis there was a marked reduction in the cystine content without any appreciable change in the total protein content of the finger-nails. With the subsidence of skin symptoms and improvement in the clinical condition, the cystine content returned to normal limits. In severe pellagrins without dermatitis (involvement chiefly of the gastro-intestinal or central nervous systems) and in partially or completely cured cases of pellagra there were no marked changes in the cystine content of the finger-nails. In the syphilitic and tuberculous group no definite changes were found whatever the nutritional state of the patient. The good effects claimed for the thiosulphate treatment of pellagra may perhaps be partly explained by the altered sulphur metabolism in this disease.

A. D. B.

ROSCOE (Margaret Honora). **Note on the Incidence of Dermatitis among Rats deprived of Vitamin B_2.**—*Biochem. Jl.* 1933. Vol. 27. No. 5. pp. 1533–1536. [14 refs.]

——. **The Vitamin B_2 Content of Various Materials compared by their Power to promote Growth and to cure Dermatitis Respectively.**—*Ibid.* pp. 1537–1539.

——. **The Heat-Stability of Vitamin B_2. III. The Rate of Destruction at Various Reactions of Vitamin B_2 contained in Different Materials.**—*Ibid.* pp. 1540–1544. [14 refs.]

(1) The appearance of dermatitis in rats fed upon vitamin B_2-deficient diets is very irregular. The reason for this irregularity is not known and an attempt to solve the problem is described. (2) An account is given of experiments designed to show whether vitamin B_2 contains two separate factors, one for the promotion of growth and the other for the prevention or cure of dermatitis. (3) The heat-stability of vitamin B_2 is discussed.

Paper 1.

"Dermatitis has occurred in 108 out of the 191 rats fed on vitamin B_2-deficient diets in this laboratory during the past seven years. The average time taken for symptoms to develop was 10 weeks.

Time of year, weight increase and various alterations in the diet were without effect on the occurrence of symptoms."

Paper 2.

"The daily doses of yeast extract, egg-white filtrate or meat needed to cure dermatitis associated in young rats with vitamin B_2-deficiency were shown to be proportional to the daily doses needed to promote a given weight increase. This was also true of the yeast extract after it had been treated in acid or alkaline media. Thus no support was found for the theory postulating the existence of separate dietary factors responsible respectively for preventing and curing dermatitis and for promoting growth."

Paper 3.

". . . vitamin B_2 was found to be relatively heat-stable in acid solution and the rate of destruction to be increased rapidly with increasing alkalinity." *A. D. B.*

FLINKER (Robert). Pellagra und progressive Bulbärparalyse. [**Pellagra and Progressive Bulbar Paralysis.**]—*Schweiz. Med. Woch.* 1934. May 5. No. 18. pp. 394–395. With 2 figs.

The author describes a case of pellagra of long standing in which bulbar paralysis developed as a result, the author believes, of the pellagra.

A. G. B.

HARRIS (Leslie J.). Deaths from Pellagra. [Correspondence.]—*Brit. Med. Jl.* 1933. Dec. 9. pp. 1096–1097.

HOLM (Sigrid). Et tilfaelde af sekundaer pellagra.—*Hospitalstidende.* 1934. Jan. 2. Vol. 76. No. 1. pp. 21–24. With 2 figs. & 1 chart.

YELLOW FEVER.

DUDLEY (Sheldon F.). **Yellow Fever as seen by the Medical Officers of the Royal Navy in the Nineteenth Century.**—*Proc. Roy. Soc. Med.* 1933. Feb. Vol. 26. No. 4. pp. 443–456 (United Services Sect. pp. 7–20).

The author has searched the old Naval Reports for records of yellow fever and has gleaned much that is of interest and value. His practical conclusions are that the incubation period may sometimes exceed a week, the case fatality in groups may vary from nothing to 60 per cent., West African strains are as a rule more fatal to Europeans than American strains.

Contagiousness.—Naval medical officers in the nineteenth century were chiefly non-contagionists. The contagionists pointed to the high mortality among doctors; *e.g.*, PLAZY says that at San Domingo in 1802, 208 out of 300 doctors died. The author thinks that recent laboratory cases described by LOW and FAIRLEY [this *Bulletin*, Vol. 28, p. 290] in which yellow fever was contracted in England without the possibility of mosquito transmission, by persons who handled infected blood, suggest the likelihood of direct transmission to doctors in the old days. As he writes, "if direct transmission was more than an exceptional unnatural event a densely crowded ship was the place to find it."

Aetiology.—Exposure at night was thought to be specially dangerous and as much effort was made to prevent men exposing themselves to the night air by sleeping on the upper deck as is now made to encourage them so to do. Sexual and alcoholic excess was also held accountable, this doubtless because in drinking dens and brothels the sailors came in contact with both native reservoir and insect vector. Chill and fatigue were blamed because of the high rate of fever among men employed in boats away from the ship; they would often camp in pestilential creeks or native villages and go down with fever on return to the ship. The danger of the proximity of swamps was recognized but the occurrence of yellow fever in time of drought was a mystery till the discovery that storage of water brought the carrier.

The following extract is of special interest :—

"I have picked out the following story as one which illustrates practically all the peculiar points in the epidemiology of yellow fever at sea. I must first explain that it was, and to a less extent is, the fashion to moor old hulks at Naval Bases to act as depôts, where men await an opportunity to join their ships, or to take passage home, or to proceed to other stations. In 1865 the "Isis" was the depôt ship at Sierra Leone. This year yellow fever is said to have destroyed 27 per cent. of the European colony. The first case of yellow fever in the "Isis" was reported on September 28. Then follows a description of case after case of men passing through the ship and contracting the disease. Among these was the surgeon of the "Rattlesnake" who was attending the sick in the "Isis," her own doctor being dead of the disease. The surgeon of the "Rattlesnake" went back to die in his own ship, and apparently infected her, since yellow fever broke out in epidemic form and continued until the "Rattlesnake" went north on December 24. On December 26 the authorities, realizing that the "Isis" was infected, decided to have her cleaned out, and 112 men from H.M.S. "Bristol" were told off for this duty. This party worked on board the "Isis" for two days from 7 a.m. to 10 p.m. The first case in the "Bristol" appeared on December 31, altogether 39 cases, 25 of which died, were recorded. Everyone of these cases was among the 112 men who had been on board the "Isis"; there was no case of fever of any kind reported among the 400 men in the "Bristol" who had not boarded the "Isis." . . .

" [Surgeon] Ayre [of the "Bristol"] could suggest no source of infection of the "Bristol's" victims, except possibly the rain water tanks of the "Isis," from which some of the "Bristol's" working party had drunk. He little realized that these tanks did contain the solution of his problem. These old depôt hulks used to be roofed in and the water from the roofs was collected in tanks for washing purposes. The tanks formed ideal aquaria in which a home-grown stock of the *Aëdes* could be maintained, however far the ship was moored off the beach."

The story needs no commentary.

Incubation period.—The nature of ships allows of a reliable estimate of incubation periods. Many naval records show that the incubation of yellow fever is not infrequently over a week. The "Bristol" victims of the "Isis" went sick over a period between December 31 and January 12, "a range of incubation of from three to fifteen days," and in seven instances the period must have exceeded seven days. This and other instances show that the incubation period of yellow fever does sometimes exceed a week, though the International Sanitary Covention assumes that the incubation never exceeds six days.

Diagnosis.—During the seventies the diagnosis of yellow fever was rarely made in the Navy unless the patient had black vomit and jaundice. In 1866 and 1867 DONNET of the Royal Naval Hospital, Jamaica, showed how yellow fever differed from malaria, that it was not a remittent fever, that one attack caused immunity, relapse never occurred and quinine was useless. He further maintained that the characteristic and essentially pathognomonic symptom was albuminuria. After his time many naval surgeons laid stress on albuminuria and absence of response to quinine in the recognition of the disease.

Morbidity and Fatality.—A table of mortality from disease in the Royal Navy, 1825–45, shows that on the West African station it was 6 times as great as at home and 3 times as great as in the West Indies, the other yellow fever station. The excess of deaths, the author says, was caused almost entirely by yellow fever. The deaths in any year tended to be concentrated in one or two ships; striking instances are given. This is described as an "all or nothing" effect, a ship either had a colossal death rate or escaped lightly. In 1845, of 121 deaths in 28 ships 74 occurred on the *Eclair*. She became infected at Sierra Leone, carried infection to Bona Vista in the Cape Verde Islands, left for Madeira and reached England on September 28 by which date 4 medical officers had succumbed, followed by two at Portsmouth in early October, which illustrates the risk to medical officers and shows that the insect vectors could remain active in that month in the warmth between decks. The *Eclair* had a crew of 120 men of whom 74 died, so that the case fatality could not have been less than 61 per cent. In later years, however, there were ship epidemics, probably yellow fever, accompanied by little or no fatality. A study of these epidemics shows that yellow fever varies greatly in virulence. Table III shows that the fatality was significantly higher in the West African than the West Indies station.

Table III.—Tropical Fever, Case Fatality. "Recorded" Yellow Fever.

Period.	*Station.*	*Cases.*	*Deaths.*	*Fatality %*
1856–70	W. Africa	223	126	56·5±1·9
1856–70	W. Indies	1,548	585	37·8±0·8
1871–88	,,	151	56	37·1±2·7
1856–88	S. America	120	34	28·3±2·7

In another table are analysed the tropical fever statistics of the West Indian Squadron in 1861, a bad year, with a case fatality of 45 per cent. Here again the " all or nothing " phenomenon comes out : four ships out of 25 accounted for 129 deaths out of 144 reported. The " recorded " fatality in these 4 ships varied from 24 to 80 per cent. ; it is believed, however, that these divergencies depended more on the diagnosticians than on the virus ; mild cases were recorded by some more than others. For similar reasons the author suggests that the real case fatality approached 20 rather than 45 per cent. CARTER states that the fatality among Europeans in North and Central America in the present century, when diagnosis has been reliable, has rarely exceeded 10 per cent. and in Panama in the worst epidemic that CARTER had experience of it was 16·6 per cent. In West Africa yellow fever has always been more deadly to Europeans than in the New World.

Racial Immunity.—The immunity of the West African native to yellow fever is well known. The Krumen were used as attendants on the sick because they never contracted the fever or, if they did, the attack was mild. This immunity is probably an acquired character.

West African Origin of Yellow Fever.—This subject was discussed at length by CARTER in his monograph, and he concluded that West Africa was the original focus. Dudley corroborates CARTER and brings additional evidence for this origin. He cites Sir Francis DRAKE's expedition in 1585 in which he believes yellow fever was contracted at the Cape Verde Islands, and another in 1553 ; here 100 of 140 sailors died of an epidemic in their ship off the mouth of the Benin river and in a little over a month. Dudley argues that this cannot have been anything else but yellow fever, and points out that the locale is near the recently discovered focus in Ibadan, perhaps " the one place in the world where yellow fever can now maintain a permanent endemicity." No epidemics of this kind were reported at that period from the New World. *A. G. B.*

KERR (J. A.) & PATIÑO CAMARGO (Luis). Investigaciones sobre fiebre amarilla en Muzo y en la " región de Santander." [**Yellow Fever in Muzo and the Santander Region.**]—Reprinted from *Rev. de Higiene.* Bogota. 1933. Vol. 2. No. 3. 32 pp. With 2 maps & 1 fig. [10 refs.]

The Department of Santander (Colombia) has been invaded by yellow fever on three occasions: Bucaramanga and its environs in 1910–12 and in 1923, Socorro and the vicinity in 1929. By the " Santander Region " is meant the central hilly district of the Department, some 1,000 to 1,300 metres above sea-level.

The authors visited the district, searched for Aëdes, and took samples of blood (25 cc.) from over 1,000 persons, especially of school children who had been born and brought up in the place. The sera were sent to the Yellow Fever Laboratory of the Rockefeller Foundation in New York for the protection test to be carried out.

As a result of their investigations they have come to the conclusions that yellow fever has been for many years endemic in the rural parts of the Muzo municipality ; also that in spite of *Aëdes aegypti* being very abundant, yellow fever has not been present among those living along

the banks of the Magdalena River during the past 15 years, nor in the Cúcuta valleys in the past 20 years. In other words during this period there has grown up a large non-immune population. They do not believe that yellow fever has been re-introduced into the region during the past 15 years but that it has remained endemic there, not in the townships but in the rural areas, and this district should consequently be regarded as a dangerous focus whence infection may be propagated to the lower-lying and more readily infectable parts of the country.

H. H. S.

DUFF (D.). **A Note on Yellow Fever Control in the Gold Coast and the Present Situation.**—*Gold Coast Rep. on Med. Dept. for Year 1932–33.* Appendix 6. pp. 88–93.

A general account of the author's experience of yellow fever control on the Gold Coast. The routine measures in constant use are :—

" (*a*) Mosquito destruction in the ports and all the larger towns, and beyond these areas where we can place reliable sanitary staff.

" (*b*) Segregation of susceptibles (Europeans) in residential areas with a building-free zone of at least 440 yards from the native town and the enforcement of very special rules for these areas.

" (*c*) A constant watch by all medical officers for cases of the disease, mild or otherwise, and the collection and dissemination to all stations of information concerning such cases.

" Emergency measures during an outbreak :—

" (*a*) Intensification—especially at a focus of outbreak—of the routine anti-mosquito campaign. It is assumed, as a working rule, that when a recognisable case occurs, an outbreak is going on somewhere in a mild unrecognisable form, and that a genuinely " sporadic " case cannot really occur.

" (*b*) Proclamation by law of ' infected areas ' in order to obtain emergency powers for the sanitary authority.

" (*c*) Temporary evacuation, if necessary, of susceptibles from such areas.

" (*d*) Isolation and careful screening of cases, and fumigation of houses where such cases have occurred."

With regard to their application, the introduction of a piped water supply is the most effective single measure for limiting the breeding of mosquitoes in towns, and where this is impracticable water supplies need constant supervision. The segregation of Europeans outside the native towns has been encouraged by the Government since 1908 and as a result the invaliding and mortality rates have been considerably reduced. The Syrians, however, continue to live in the native towns and are often the first to be attacked in outbreaks of yellow fever.

Every medical officer is encouraged to notify any suspicious case, and if the diagnosis is confirmed other administrations in West Africa are notified by cable.

Anti-mosquito control is based on the monthly larval index, and efforts are directed to keeping it well below 5 per cent. Yellow fever has never broken out in any centre where segregation combined with mosquito control has been practised.

With reference to air transport the author considers that it is possible to control specialized areas. Consequently there should be no difficulty in siting aerodromes so that the chance of any infected mosquitoes getting on board an aeroplane would be almost nil. The chance of a

passenger who may be incubating yellow fever being taken on board might be met by insisting that the passengers and crew should dwell in a controlled area for 6 days before departure. *E. Hindle.*

MATHIS (Maurice). Transmission expérimentale de la fièvre jaune par piqûres de stégomyies, à Paris, en janvier, février, mars 1934. [**Experimental Transmission of Yellow Fever in Paris by Bites of Stegomyia during January, February and March, 1934.**]—*C. R. Soc. Biol.* 1934. Vol. 115. No. 11. pp. 1217–1219.

Two monkeys in Paris were infected with yellow fever by the bites of mosquitoes infected respectively with the Asibi and French strains of the virus. *E. H.*

DAVIS (Nelson C.). **Transmission of Yellow Fever Virus by** *Culex fatigans* **Wiedemann.**—*Ann. Ent. Soc. Amer.* Columbus, Ohio. 1933. Sept. Vol. 26. No. 3. pp. 491–495.

Using the Asibi strain of yellow fever virus, in two experiments the author succeeded in transmitting the disease to *rhesus* monkeys by the bites of infected *Culex fatigans*.

In one experiment 14 insects were fed on the monkey 17 days after an infective blood meal, and the animal died of typical yellow fever. In another experiment 7 fed after a 20-day interval, and 8 more fed 3 days later on the same monkey, which developed fever, but recovered and was immune. In spite of these positive results this species does not seem to be an efficient host for yellow fever virus, and although in one lot of mosquitoes survival of the virus was demonstrated by injection as late as 39 days after the meal of infected blood, in many experiments there was evidence that the insects were able to free themselves from the virus. *E. H.*

SMITH (E. C.). **A Case of Sub-Acute Yellow Atrophy Clinically Suggestive of Yellow Fever.**—*West African Med. Jl.* 1933. Oct. Vol. 7. No. 2. pp. 91–93. With 2 figs. on 1 plate.

The record, including pathological details, of a case of acute yellow atrophy (or necrosis) in a West African native, in which the clinical symptoms closely resembled those of yellow fever. Post-mortem examination showed that a severe broncho-pneumonia had supervened, the toxins emanating therefrom causing further damage to an already overburdened and incompetent liver. Haemorrhages and erosions were present in the stomach, presumably as a result of passive congestion.

This condition is very uncommon in the African native and the tendency for it to simulate yellow fever should be borne in mind.

E. H.

HINDLE (Edward). **Recent Laboratory Contributions to the Control of Yellow Fever.**—*Proc. Roy. Soc. Med.* 1933. Dec. Vol. 27. No. 2. pp. 203–210 (Sect. of Trop. Dis. & Parasit. pp. 1–8).

A general account of the subject with special reference to the more important laboratory contributions to the control of yellow fever and

summarized under three headings; (1) Methods of diagnosis, (2) transmission, and (3) protection.

In the discussion on the paper Colonel S. P. JAMES agreed that the articles relating to yellow fever in the International Sanitary Convention of 1926, and the International Sanitary Convention for Aerial Navigation of 1933, did not cover all the possible risks indicated by the results of recent laboratory research, but stated that it was the practice to base such regulations on what occurred in the great majority of cases rather than on what might occur very exceptionally. *E. H.*

MATHIS (Maurice). Sensibilité du cobaye au virus de la fièvre jaune. [**The Susceptibility of the Guineapig to Yellow Fever Virus.**]—*C. R. Soc. Biol.* 1934. Vol. 115. No. 8. pp. 842–844.

The Asibi strain of yellow fever virus derived directly from infected *rhesus* has been inoculated intracerebrally into mice and guineapigs in order to determine especially whether the latter were readily susceptible to the viscerotropic virus. One of the first two guineapigs inoculated developed paralysis and was killed on the 10th day. Two guineapigs inoculated from this animal died on the 9th and 10th days, and two used for the third passage died on the 7th day. It is evident, therefore, that the guineapig is susceptible to ordinary yellow fever virus and not only to the so-called mouse neurotropic virus. Clinically the infected guineapigs were found to show a myelitis, not an encephalitis. *E. H.*

LLOYD (Wray) & MAHAFFY (Alexander F.). **The Survival of Neurotropic Yellow Fever Virus in Testicular Tissues.**—*Jl. Immunology.* 1933. Dec. Vol. 25. No. 6. pp. 471–482. With 1 fig.

Neurotropic yellow fever virus of the French strain after its 212th to 249th passages in mice, was inoculated into the testes of albino mice, and found to survive for periods up to five days.

By making passages every fourth day the virus was transferred through nine passages in the testicular tissues and retained its neurotropic character. Virus isolated from the 6th and 7th passages, respectively, in the testes of mice was found to give the same specific immunological reaction as yellow fever virus in passive immunity tests. Moreover, a *rhesus* monkey inoculated subcutaneously with the testicular virus, showed only a mild febrile reaction 26 days after the inoculation, but was immunized against the disease. *E. H.*

FINDLAY (G. M.). **The Infectivity of Neurotropic Yellow Fever Virus for Animals.**—*Jl. Path. & Bact.* 1934. Jan. Vol. 38. No. 1. pp. 1–6. With 4 figs. on 1 plate. [13 refs.]

With the object of obtaining larger supplies of neurotropic virus, the author has determined the reaction of a number of animals to intracerebral inoculation with two strains of yellow fever.

The cat, ferret, rabbit, rat, golden hamster (*Cricetus auratus*), wood vole (*Apodemus sylvaticus*), bank vole (*Evotomys glareolus*), pigeon, hen and canary showed no signs of disease. The virus was found to survive for a few days in those animals examined, up to 6 days in the

case of the rat, but there was no evidence of any multiplication, nor any histological changes in the brain. The sera of the cat, ferret, rabbit, rat, pigeon and hen were tested by the mouse protection test before inoculation and three weeks afterwards. All were found to have acquired protective antibodies against yellow fever virus.

Guineapigs, red squirrels (*Sciurus vulgaris*) and field voles (*Microtus agrestis*) developed clinical symptoms of fatal encephalitis, 17 passages being made in guineapigs and 5 in field voles. Histologically the brains of these voles showed meningeal infiltration together with scattered areas of perivascular infiltration and here and there degenerative changes in the ganglion cells, but these changes were never so extensive as in mice. Similar histological changes were also present in the infected squirrels. *E. H.*

BUDING (E.). Sur la teneur en graisses et en phosphore lipoïdique du foie chez les cobayes atteints de fièvre jaune et de spirochétose ictérohémorragique. [**The Fat and Lipoid Phosphorus in the Liver of Guineapigs infected with Yellow Fever and with Spirochaetal Jaundice.**]—*C. R. Soc. Biol.* 1933. Vol. 114. No. 38. pp. 1152–1155.

The author has studied the fatty degeneration of the liver in guineapigs infected either with yellow fever or with spirochaetal jaundice. In both diseases it was found that there is an increase in the total lipoids, accompanied by a corresponding diminution in the amount of lipoid phosphorus in the lipoid fraction. These results indicate that the superabundant fat in the liver is not produced by any transformation of the hepatic proteids. *E. H.*

NICOLAU (S.), KOPCIOWSKA (L.) & MATHIS (M.). Inclusions intranucléaires dans le système nerveux des cobayes et des souris morts de fièvre jaune expérimentale; genèse, morphologie et interprétation. [**Intranuclear Inclusions in the Nervous System of Guineapigs and Mice Dead from Experimental Yellow Fever: their Origin, Morphology and Significance.**]—*C. R. Acad. Sci.* 1934. Jan. 15. Vol. 198. No. 3. pp. 288–290.

The authors describe the intranuclear inclusions present in the nerve cells of guineapigs and mice infected with neurotropic yellow fever virus. In mice inclusion bodies were also found exceptionally in the vascular endothelium and the cells of the choroid plexus, which shows that the virus is not strictly neurotropic.

Discussing their appearance the authors consider that previous observers have not clearly demarcated between the formation of inclusions, one of the results of cellular resistance, and the oxyphile degeneration of the nucleus, resulting either from the sickness or death of the cell. *E. H.*

FINDLAY (G. M.) & BROOM (J. C.). **Experiments on the Filtration of Yellow Fever Virus through "Gradocol" Membranes.**—*Brit. Jl. Experim. Path.* 1933. Dec. Vol. 14. No. 6. pp. 391–394.

Filtration experiments were made with neurotropic and viscerotropic strains of yellow fever virus. By the use of "Gradocol" membranes

the neurotropic virus was found to have a limiting pore size of 55μμ; therefore the diameter of the virus particles is estimated to lie between 18 and 27μμ. A few experiments with a viscerotropic virus gave similar results; therefore the particles are probably within the same range of size as those of the neurotropic virus.

Relative concentration of the virus was obtained by passing suspensions through a 50μμ membrane. *E. H.*

FINDLAY (G. M.). Nouvelles expériences concernant l'immunisation contre la fièvre jaune. [**New Experience of Immunization against Yellow Fever.**]—*Bull. Office Internat. d'Hyg. Publique.* 1934. Jan. Vol. 26. No. 1. pp. 43–51.

The author gives particulars of 120 patients who have been immunized against yellow fever, including 117 Europeans, 2 Africans and one Hindu. It is of interest that neither of the Africans showed any trace of reaction after the inoculation, whilst the Hindu had a febrile reaction which lasted 48 hours. 40 persons have been immunized by the subcutaneous inoculation of serum and virus, and 80 by intradermal inoculation.

Of the 40 persons vaccinated subcutaneously one was immune before vaccination and showed no reaction; 15 had very slight reactions without fever, and 24 reacted with temperatures above 37·2°C. Only one of these cases showed any serious symptoms.

The techique of the intradermal method was worked out by experiments on monkeys. The region of the skin selected as the site of the injection, preferably the abdomen and showing no superficial vein, is carefully cleaned. Then 1 cc. of immune serum of known titre is drawn up into a sterile tuberculin syringe provided with a fine intradermic needle, similar to those used for the Schick test (about 0·45 mm. in diameter). Four inoculations of 0·25 cc. each are then made in the skin at the four angles of a one-inch square. Two hours later in the same region of the skin, at the middle of the square, an intradermal injection of 0·2 to 0·3 cc. of the virus suspension is administered. The latter is prepared by making a 1 in 10 suspension of infected mouse brain in normal human serum, and then passing it through a Seitz filter.

Out of 80 patients immunized by this method, only 30 have shown any temperature above 37·2°C. and of the 50 showing no fever, 26 had no appreciable reaction. The local reactions were extremely slight, however, and among those showing no fever, the only symptoms consisted of a slight headache, a feeling of lassitude or heaviness, sometimes shivering, often accompanied by a subnormal temperature. As a rule these symptoms appeared about 30 hours after the injection of the virus and lasted for 24 to 48 hours.

The 30 cases showing a temperature of more than 37·2°C. are divided into 3 groups:—(1) 10 cases in which the fever appeared within 48 hours of the injection; (2) 4 cases with a reaction within 48 hours followed by exacerbation later; and (3) 16 cases with a retarded reaction 4 days or more after the inoculation.

The amount of antibodies developed after intradermal inoculation is not below that following the subcutaneous method, and in view of the

much smaller quantities of immune serum required (1 cc. instead of 35 to 40 cc.) this method possesses very considerable advantages.

E. H.

FINDLAY (G. M.). **Immunization against Yellow Fever.**—*Trans. Roy. Soc. Trop. Med. & Hyg.* 1934. Mar. 12. Vol. 27. No. 5. pp. 437–464. [59 refs.]

This important paper should be read in its entirety by those interested in the subject, for although the main conclusions concerning the efficiency of the intradermal method of inoculating virus and immune serum have been published previously [see above] the present article contains many additional details and also particulars of more cases.

With reference to the neurotropic virus it is of especial interest that in the hedgehog, *Erinaceus europaeus*, the intracerebral inoculation of this type of yellow fever virus may produce necrotic changes in the liver. It was found possible to infect mice and monkeys by introducing the neurotropic virus in the nostrils, encephalitis being produced. Up to the end of 1933, the author had immunized 200 persons against yellow fever with varying doses of mouse-fixed neurotropic virus and human immune yellow fever serum, of which 86 or 43 per cent. reacted with a temperature above 99°F. with varying symptoms, which are described in detail. Virus was detected in the circulating blood in 2 out of 16 cases, and with the object of preventing the occurrence of virus in the blood and also reducing any reaction, some of the persons were inoculated subcutaneously with 5 cc. of immune serum in addition to the ordinary intradermal injections. The specificity of the mouse protection test for immune bodies to yellow fever is again brought out by the author's results, for patients recovered from Rift Valley fever, dengue, and also a form of infective jaundice in Barbados, all failed to give any protection. In addition, of 26 Europeans resident in West Africa, only one gave protection and he had a history of an attack of infective jaundice. 22 residents in Great Britain all failed to show the presence of immune bodies to yellow fever while 9 persons with a history of the disease all gave protection. On the other hand the sera of 115 persons examined after immunization were all positive, the immune bodies appearing after 8 to 9 days, and attaining their maximum titre in from 4 to 5 weeks. After 10 to 11 months the titre decreased, but immune bodies could still be detected up to at least 16 months after inoculation.

Both the neurotropic and viscerotropic strains of yellow fever virus, in the presence of 1 in 100,000 methylene blue, were inactivated by exposure to a pointolite lamp but the antigenic activity was destroyed.

E. H.

SELLARDS (A. W.) & LAIGRET (J.). Durée de l'immunité consécutive à la vaccination contre la fièvre jaune. [**The Duration of Immunity following Yellow Fever Vaccination.**]—*C. R. Acad. Sci.* 1934. Mar. 12. Vol. 198. No. 11. pp. 1086–1087.

The sera of two patients who were vaccinated by the inoculation of small doses of mouse virus without immune serum, have been tested after intervals of 10 and 25½ months respectively. Both were found to protect mice against at least 640 lethal doses of the virus. *E. H.*

LAIGRET (J.). Le controle des vaccinations antiamariles par l'épreuve de protection sur souris. [**The Control of Yellow Fever Vaccination by Protection Tests in Mice.**]—*Arch. Inst. Pasteur de Tunis.* 1934. Mar. Vol. 23. No. 1. pp. 43–47.

The author recommends the intracerebral protection test in mice, described by THEILER, in order to determine the protective power of the serum of vaccinated persons. *E. H.*

SOPER (Fred L.) & SERAFIM (J.), Jr. **Note on the Breeding of *Aëdes* (*Taeniorhynchus*) *fluviatilis*, Lutz, in Artificial Water-Deposits.**—*Amer. Jl. Trop. Med.* 1933. Nov. Vol. 13. No. 6. pp. 589–590. With 1 fig.

When mosquito larvae collected in the Valle do Chanaan, Espirito Santo, Brazil, where yellow fever was epidemic (*ante*, p. 77) were being classified, larvae of *Aëdes fluviatilis* were found among specimens taken from cement ant-rings. Moreover, rock-hole breeding places of this species were found within 30 yards of houses and adults were captured there. Since *A. fluviatilis* has been shown by DAVIS and SHANNON to transmit yellow fever readily in the laboratory these observations have significance. [See this *Bulletin*, Vol. 28, p. 727. In 11 trials there were at least 8 infections.] *A. G. B.*

KUMM (Henry W.). **Mosquitos breeding in Bromeliads, at Bahia, Brazil.**—*Bull. Entom. Res.* 1933. Dec. Vol. 24. Pt. 4. pp. 561–573. With 12 figs. & 2 coloured plates.

PERYASSÚ (1930) has stated that larvae of *Aë. aegypti* are sometimes seen in Bromeliads and that they had been found here 11 times in 1,194 collections. Effort has been made during yellow fever campaigns to destroy these plants; hence this investigation, of which it will be sufficient to give the conclusions :—

" Twenty-one collections of larvae and pupae from Bromeliads, growing in trees or on the ground, were made in São Salvador, the capital of the State of Bahia, Brazil. Four species of *Microculex* and one Sabethine were bred out. Of these, one new species and certain new forms are described. The new species is called *Culex* (*Microculex*) *davisi* in honour of Dr. Nelson C. Davis, at whose suggestion this study was first undertaken. Since no *Aëdes* (*Stegomyia*) *aegypti* were found, it would appear that Bromeliad breeding is probably of no importance from the standpoint of a yellow fever control campaign in this region." *A. G. B.*

KERR (J. A.). **Studies on the Abundance, Distribution and Feeding Habits of Some West African Mosquitos.**—*Bull. Entom. Res.* 1933. Dec. Vol. 24. Pt. 4. pp. 493–510. [14 refs.]

The work here recorded was carried out during 1930–1931, chiefly in and around Lagos, in order to gain further knowledge of mosquitoes " found experimentally to be vectors of yellow fever."

Lists are given of these species, and of those " non-lethal to the virus . . . but which have not been shown to be capable of transferring it by their bites." The methods employed to obtain the information desired were :—catching mosquitoes inside houses by day ; catching at night with human bait during three hours commencing at sunset (" ' standard ' night catches ") ; and catching throughout the night, from sunset to sunrise, by two boys at the same spot, the mosquitoes

caught during each hour being segregated. In view of previous observations by others in the same locality, the author, being specially concerned with species that attack man, paid little attention to the rearing of larvae. Among the results obtained, which are set forth in a series of tables and discussed in the text, a few points may be noted.

In daytime catches inside native houses from 30th April to 24th July, 1930, *Anopheles gambiae* (*A. costalis*), that well-known African malaria-carrier, which does not convey yellow fever, was enormously in the majority—12,098 individuals, out of a total of 14,554 belonging to more than eleven species ; by comparison, the number (24) of *Aëdes aegypti* taken seems well-nigh negligible ; the latter species was also rarely caught by night out-of-doors. *Aëdes africanus* and *A. luteocephalus*, common West African tree-hole breeders, and experimental vectors of yellow fever, also seem to be conspicuous by their absence inside houses near Lagos, though aggressive in the open during the first hour and a half after sunset. *Eretmopodites chrysogaster*, another experimental vector, which breeds by choice in small collections of water in fallen leaves among cocoa-plantations, is believed on the evidence obtained not to bite man in nature. *Mansonia africana*, also an experimental vector and a notorious pest which feeds by preference on human blood, not only enters houses in search of food but bites freely out-of-doors the whole night through. *Mansonia uniformis*, though closely resembling *M. africana* both in appearance and habits, belongs to the group of mosquitoes the members of which may retain the yellow fever virus for life, though apparently incapable of acting as vectors.

E. E. Austen.

PHILIP (Cornelius B.). **Mosquito Species breeding in "Test" Water Containers in West Africa.**—*Bull. Entom. Res.* 1933. Dec. Vol. 24. Pt. 4. pp. 483–491.

In continuation of similar work by DUNN (this *Bulletin*, Vol. 25, p. 273) during the greater part of the dry and commencement of the wet season, in and about the compound of the West African Yellow Fever Commission near Lagos, the present author on the same spot, using bamboo sections as containers, made continuous observations on mosquito-breeding during the wet season and beginning of the dry. Prior to final acceptance, the contrasting seasonal data thus obtained must obviously be checked by the experience of several years.

The ten containers used by Philip, which were filled with rain-water so long as this was available, were with three exceptions deposited in the same places as those employed by DUNN and were examined at five-day intervals. Fifteen species—all Culicines—availed themselves of the breeding facilities afforded, and, as was also found by the earlier worker, *Aëdes aegypti* occurred more frequently than all the others combined ; while, as before, its larvae were most numerous in a shaded container 33 yards from an animal house. *E. E. A.*

MOUNTJOY (J. E.). **An Observation on Mosquito Breeding in Pawpaw Trees.**—*East African Med. Jl.* 1933. Oct. Vol. 10. No. 7. pp. 214–216. With 4 figs.

Stimulated thereto by a report that the cutting down of a living papaw [*Carica papaya*] tree had caused the liberation of a quantity of water from within the trunk or one of the branches, the author ordered

a careful examination to be made of the papaw trees in Kigoma, Tanganyika Territory. Out of eighteen of these trees which were found to contain water—in one case between 1½ and 2 gallons—mosquito larvae, both *Culex* and *Aëdes* but chiefly the latter, were discovered in fourteen. In an old papaw tree, the disappearance of the transverse septa within the trunk may allow a large volume of water to pass down and accumulate, possibly below the level of the ground ; and since the orifice of ingress, usually in a fork or where a branch leaves the trunk, may be too small to admit an exploratory ladle, an important source of mosquito breeding may easily be overlooked. *E. E. A.*

BLISS (A. Richard), Jr. & GILL (Jessie May). **The Effects of Freezing on the Larvae of** *Aëdes aegypti*.—*Amer. Jl. Trop. Med.* 1933. Nov. Vol. 13. No. 6. pp. 583–588. [11 refs.]

The development and extension of aerial transport has caused increased attention to be paid to the possibility of the conveyance by this means of adult, and possibly infected, *Aëdes aegypti*, although rapid carriage would not necessarily assist the insect to establish itself in a temperate climate.

In order to discover whether the larval stage of *A. aegypti* can survive being embedded in ice, " and, if so, for how long," the authors froze two batches of larvae in solid ice for from two to eleven, and ten to sixteen hours respectively. Exposure to this treatment for eleven hours or more proved fatal ; but larvae encrusted in ice for not longer than ten hours, and then gradually thawed, revived and produced adults in about the same time as controls. Since the egg-stage of this species is known to be more resistant to freezing, should *A. aegypti* be capable of surviving where its larvae are frozen solid in winter, such survival must depend " upon the eggs, or the hibernating females, or both."

E. E. A.

MONTEIRO (J. Lemos). Sobre possiveis vehiculadores do virus amarillico. (A proposito de um trabalho de H. Kumm e M. Frobisher.)—*Brasil-Medico.* 1933. Apr. 15. Vol. 47. No. 15. pp. 257–258.

MONTEIRO (J. Lemos) & TRAVASSOS (J.). A reacção de fixação do complemento na determinação de focos e no diagnostico retrospectivo da febre amarella.—*Brasil-Medico.* 1933. Apr. 29. Vol. 47. No. 17. pp. 298–302.

RUSSELL (Frederick F.). Permanent Value of Major Walter Reed's Work on Yellow Fever.—*Amer. Jl. Public Health.* 1934. Jan. Vol. 24. No. 1. pp. 1–7. [21 refs.]

RELAPSING FEVER AND OTHER SPIROCHAETOSES.

MATHIS (C.) & DURIEUX (C.). Fréquence à Dakar de la spirochétose récurrente à tiques. [**The Frequency of Tick Fever at Dakar.**]—*Bull. Acad. Méd.* 1934. Apr. 17. 98th Year. 3rd Ser. Vol. 111. No. 14. pp. 528–532.

Three out of ten natives at Dakar, inoculated with the *crocidurae* strain of *Spirochaeta duttoni*, showed no reaction whatever; six had a single febrile attack without relapses, and only one out of the ten showed a typical attack of relapsing fever. These results support the view that the disease is relatively common, but not often recognized.

The examination of the local fauna showed that many of the rodents can serve as reservoirs of infection, in addition to *Crocidura stampflii*. Out of 18 lots of rats comprising 80 animals, 13 lots were infected as tested by the inoculation of blood or brain emulsion into mice or rats. The results were as follows:—

Epimys decumanus	(5 animals);	1 lot; positive
„ *alexandrinus*	(10 animals);	3 lots; all positive
„ *rattus*	(29 animals);	6 lots; 1 positive
„ *golonda campanae* ...	(15 animals);	3 lots; 3 positive
„ *coucha*	(13 animals);	3 lots; 2 positive

The common wild mice *Mus musculus gentilis*, and *Mus musculus spretus*, were only rarely infected, and out of 11 lots, comprising 65 individuals, the spirochaete was only found 4 times in the brain, whilst the examination of the blood in 9 lots of 5 each (45 individuals) was uniformly negative.

Out of 34 *Crocidura stampflii*, divided into 9 lots, inoculation of the blood was positive in 6 cases and of the brain in 4 cases, and it is evident that this animal is the most important active reservoir of the infection since its blood so frequently contains spirochaetes.

The authors also give figures showing the extreme abundance of the transmitting agent, *Ornithodorus erraticus*, in Dakar and its neighbourhood, and from their observations it would seem that relapsing fever must play an important part in the pathology of the district. In nine months from April to December 1933, they were able to diagnose 26 human cases of the disease. *E. Hindle.*

MATHIS (C.), DURIEUX (C.) & ADVIER (M.). Transmission naturelle et expérimentale à l'homme du spirochète infectant dans la nature, à Dakar, la tique: *Ornithodorus erraticus* vel *marocanus*. [**Natural and Experimental Transmission to Man of the Spirochaete naturally infecting the Tick,** *Ornithodorus erraticus* **vel** *marocanus*, **at Dakar.**]—*Ann. Inst. Pasteur.* 1934. Feb. Vol. 52. No. 2. pp. 166–178. With 4 charts.

Details of the results of feeding *Ornithodorus erraticus* infected with Dakar relapsing fever, on patients undergoing pyrotherapeutic treatment. It is of interest that two of the patients bitten by ticks failed to become infected, as tested both by microscopical examination of the blood and also by subinoculation into white mice. Yet the same batches of ticks subsequently produced infection when fed on other patients.

The author's results confirm those previously described as to the identity of this infection with *S. duttoni*, but in Dakar *O. erraticus* takes the place of *O. moubata* as the transmitting agent. [See this *Bulletin*, Vol. 29, p. 555; Vol. 30, p. 14, and Vol. 31, p. 87.] *E. H.*

ANDERSON (Charles) & WASSILIEFF (A.). Sur un nouveau spirochète récurrent du type *Hispanicum* rencontré chez *Ornithodorus erraticus* du Sud-Tunisien. [**A New Relapsing Fever Spirochaete of the *Hispanicum* Type found in *Ornithodorus erraticus* from South Tunis.**] —*Arch. Inst. Pasteur de Tunis.* 1933. Nov. Vol. 22. No. 3. pp. 350–363. With 6 charts & 1 fig.

Specimens of *Ornithodorus normandi* and *O. erraticus* collected mainly from burrows of *Meriones shawi* in various regions radiating from Ben-Gardan, were tested for their infectivity to guineapigs. *O. erraticus* was found to be infected with a spirochaete which was transmissible to guineapigs both by the bites of these ticks and also by the inoculation of ground-up suspensions of their contents. This spirochaete, although belonging to the general group *hispanica,* was found to differ in its cross-immunity reactions from a strain of *S. hispanica* isolated from a case of relapsing fever in Menzel-Temime, Tunis, and also from strains of *S. duttoni* and *S. normandi.* The lytic power of the serum was also tested, with similar results.

The virus seems to be highly pathogenic to man. The first patient, who received a conjunctival inoculation, became infected after an incubation period of 9 days, and died on the 27th day. The second patient, inoculated subcutaneously, also showed an incubation period of 9 days, then a severe febrile attack of 4 to 5 days, with numerous spirochaetes in the blood, followed by relapses during which spirochaetes reappeared in the blood unaccompanied by febrile symptoms. A specimen of *Meriones shawi* inoculated with this strain showed no visible spirochaetes in its blood, but was infectious to guineapigs. On the other hand, a porcupine inoculated with the same virus showed spirochaetes in its blood after an incubation period of 10 days. There seems little doubt that *Meriones shawi* is the natural reservoir of this strain of relapsing fever. *E. H.*

DELANOË (P.). Au sujet de la présence chez l'ecureuil de Gétulie d'un spirochète sanguicole, probablement récurrent, différent du spirochète hispano-marocain. [**Concerning the Presence of a Blood Spirochaete, probably a Strain of Relapsing Fever, Different from *S. hispanica,* in the Getulie Squirrel.**]—*Bull. Soc. Path. Exot.* 1933. Dec. 13. Vol. 26. No. 10. pp. 1246–1248.

The author has found a blood spirochaete in Getulie squirrels from Agadir. Guineapigs, as well as *Meriones shawi* and the white rat, were found to be refractory to infection with this strain ; therefore it differs from *S. hispanica.*

White mice could be infected with difficulty, but only showed rare spirochaetes in the blood for one day. Grey mice (*Mus musculus far* Cabrera, 1931) were also inoculated and found to be more susceptible to the infection, although even in this species few spirochaetes appeared in the blood. *E. H.*

DELANOË (P.). L'ecureuil de Gétulie, *Atlantoxerus getulus* L., 1758, est-il un réservoir du spirochète hispano-marocain, *Sp. hispanicum* Nicolle et Anderson 1928 ? [**Is the Getulie Squirrel, *Atlantoxerus getulus* a Reservoir of *S. hispanica* ?**]—*Bull. Soc. Path. Exot.* 1933. Dec. 13. Vol. 26. No. 10. pp. 1244–1246.

Six young Getulie squirrels were inoculated either intraperitoneally or subcutaneously with large doses of two strains of *S. hispanica.*

None of the squirrels showed any signs of infection, and the inoculation of their blood, and in four instances the central nervous sytem, into guineapigs gave negative results.

If, however, the spirochaetes were inoculated intracerebrally into these squirrels, they could persist in the brain for at least three months and probably longer. However, the author points out that as this species is refractory to ordinary subcutaneous inoculation, which would be the method of infection by the bite of an infected arthropod, it is not likely to be a reservoir of this spirochaete.

With regard to the strain of *S. hispanica* found by BLANC and his collaborators [*ante*, p. 87] in lice collected from these squirrels, the author is of the opinion that the lice must have acquired the infection from some other rodent. *E. H.*

DELANOË (P.). La belette, *Putorius vulgaris* L., réservoir du spirochète hispano-marocain. [**The Weasel** *Putorius vulgaris* **as a Reservoir of the Spanish-Moroccan Spirochaete.**]—*Bull. Soc. Path. Exot.* 1933. Dec. 13. Vol. 26. No. 10. p. 1249.

A young weasel, caught in Morocco, was found to contain numerous spirochaetes in its blood, which when inoculated into 3 guineapigs produced typical infections of *S. hispanica*.

The weasel showed two attacks when spirochaetes were present, one of 3 days and the other of 5 days duration, with an interval of 2 days. On the 13th day the animal was killed and its blood inoculated into guineapigs with negative results. The central nervous system, however, still contained the virus, for 4 out of 5 guineapigs inoculated with a brain suspension became infected. *E. H.*

i. COLEMAN (George E.). **Relapsing Fever in California. I. The Experimental Disease.**—*Jl. Infect. Dis.* 1933. Nov.–Dec. Vol. 53. No. 3. pp. 337–354. [44 refs.]

ii. ——. **Relapsing Fever in California. II. Immunity.**—*Ibid.* 1934. Jan.–Feb. Vol. 54. No. 1. pp. 1–22. [38 refs.]

i. A detailed account of relapsing fever in California based on the study of three strains isolated from human cases.

Two of the patients were bitten by ticks (species unknown) at Brookway, Lake Tahoe, and in both clinical relapsing fever developed. The blood contained spirochaetes and was infectious by direct transmission to monkeys and rats. The third strain was obtained from the author's own blood and as in the case of the other two was probably a relapse strain. The source of this infection is a little obscure but it probably originated in the laboratory.

A study of the experimental disease in mice showed that all three Californian strains were practically identical though one was more virulent than the other two. Spirochaetes appeared in the blood after 18 hours to 3 days and there were usually two or three relapses, sometimes four and rarely five. The first attack lasted two to five days and the first two relapses from one to ten days. With small doses there were very few deaths, but with larger doses there was a high mortality. A mixture of 0·5 cc. infected blood, collected during the first relapse, and 8 cc. of defibrinated sheep's blood, was found to be infectious after 140 days at 0°C. Symptoms due to lesions of the nervous system were observed in seven mice, but whether the result of the infection or not is a little uncertain. The disease produced in mice by the Californian

strains was found to be more severe than that caused by *S. novyi*, and possibly than that caused by *S. duttoni*. The blood of two adult guineapigs on the 22nd and 23rd days, respectively, infected mice, although the daily microscopical examination of these guineapigs was uniformly negative. The serum of these animals showed no protective properties against infection in mice. With the Californian strains, in the absence of spontaneous agglutination, little if any difference is shown in the virulence of blood taken during the primary attack and blood taken during the first three relapses.

ii. The problem of immunity in relapsing fever infections is discussed in detail with special reference to the three Californian strains. Unlike the majority of results recorded, the author found that immunity of variable duration followed the injection of spirochaetes, no matter whether the test inoculations were made with blood from the same stage of the disease as that which produced immunity, or from a different stage. Consequently, there is cross immunity between homologous spirochaetes in blood from different stages of the disease.

In vitro experiments with serum gave only inconclusive results. The inoculation of immune serum into normal mice only twice conferred absolute immunity, but in some instances caused considerable delay in the development of infection, though other mice were wholly unprotected. Cross protection was obtained between two of the Californian strains and there is little doubt that all three are identical. *S. novyi* and *S. duttoni* were found to belong to different groups from that of the Californian strains as judged by cross-immunity tests, although there may be some relationship between the latter and *S. novyi*. However, the author concludes that in his opinion such tests are not wholly reliable for the differentiation of species or groups of relapsing fever spirochaetes. *E. H.*

KEMP (Hardy A.), MOURSUND (W. H.) & WRIGHT (Harry E.). **Relapsing Fever in Texas. II. The Specificity of the Vector,** *Ornithodorus turicata*, **for the Spirochete. III. Some Notes on the Biological Characteristics of the Causative Organism.**—*Amer. Jl. Trop. Med.* 1934. Mar. Vol. 14. No. 2. pp. 159–162; 163–179. With 2 figs. [18 refs.]

The first paper deals with transmission experiments, with *Ornithodorus turicata* and strains of *Spirochaeta novyi*, *S. kochi*, *S. duttoni* and *S. recurrentis*.

In feeding experiments none of these four strains could be transmitted from rat to rat through *O. turicata*. Moreover these spirochaetes died out in the tick within a week after being ingested, as tested by inoculation of their contents into rats. It is evident, therefore, that the Texas strain of relapsing fever transmitted by this tick, differs in this respect from the four other strains tested.

The second paper concerns observations on the biology of the spirochaete of Texas relapsing fever. The spirochaetes were found to be unable to pass through a Berkefeld N candle or a Seitz filter at 40 mm. negative pressure. Cultivation experiments, using Noguchi's medium and also blood and serum mixture, both aerobic and anaerobic, were uniformly negative. The virulence of the strain was greatly increased by rapid passage using the blood as soon as it showed spirochaetes. White rats, mice and *rhesus* monkeys were very susceptible, but guineapigs and rabbits gave varying results. Persistence of the virus in the brain of rats over long periods of time was not observed.

The spirochaete was found to be unable to penetrate the unbroken skin of young white rats, but these animals were infected by eating material contaminated with virulent spirochaetes. It is of especial interest that the blood during the negative intervals between the attacks was highly infective, and that very small quantities of such blood produced positive results earlier and gave more pronounced infections than larger amounts of blood.

In three strains of spirochaetes from different sources in Texas, which were identical in cytolytic tests, one failed to cross-immunize with the other two. In white rats the immunity was found to persist for at least 10 months after infection. Active immunity was produced in rats by the intraperitoneal inoculation of spirochaetes killed by heat. Passive immunity was conferred by inoculation of hyperimmune sera. Hereditary immunity was not observed in the small number of rats examined.

[These two papers are an extension of the author's previous work [*ante*, p. 86] and tend to support BRUMPT's view [*loc. cit.* and below] that the spirochaete of Texas relapsing fever is biologically distinct from *S. novyi*.] *E. H.*

BRUMPT (E.). Essai de transmission, par l'*Ornithodorus turicata*, d'une souche de *Spirochaeta novyi*, ayant subi plus de 3,000 passages sur rats. [**Attempts to transmit a Strain of** *Spirochaeta novyi* **after more than 3,000 Passages in Rats, by Means of** *Ornithodorus turicata*.]—*C. R. Soc. Biol.* 1934. Vol. 115. No. 6. pp. 600–602.

Nymphs of *Ornithodorus turicata* were fed on rats infected with a strain of *S. novyi* after more than 3,000 passages in these animals. The contents of these ticks were infective 2 days later but not after 3 weeks, and all attempts to transmit the infection by the bites of these ticks were uniformly negative. Consequently the author considers that either *S. novyi* is not transmissible by this species of tick, in which case it is distinct from *S. turicatae*; or that it has lost its power of developing in the tick as a result of being maintained in rats since 1906. The latter hypothesis being incapable of verification, it is considered that the name *S. turicatae* should be maintained [see above p. 86]. *E. H.*

SCHWETZ (J.). Note préliminaire sur la recherche des spirochètes chez les rats et les souris de Stanleyville. [**Spirochaetal Researches in the Rats and Mice of Stanleyville.**]—*Bull. Soc. Path. Exot.* 1933. Nov. 8. Vol. 26. No. 9. pp. 1140–1144. With 1 fig.

The examination of more than 500 *Rattus rattus frugivorus*, the common grey house rat of Stanleyville, has never resulted in the discovery of any blood spirochaetes. On two occasions *Spirillum minus* was found in splenectomized rats. Spirochaetes were found in the bladder of 23 out of 190 rats. Their nature is left in doubt, for the author states that they were never found in the kidneys and seemed to differ morphologically from *Leptospira icterohaemorrhagiae*. Moreover, 25 guineapigs inoculated with the urine and organs of 17 rats showed no signs of infection.

Concerning mice, 71 *Arvicanthis striatus*, 37 *Lophuromys ansorgei* and *L. laticeps*, 26 *Oenomys bacchante editus*, and 2 *Leggada grada*, were examined with negative results. *E. H.*

TODA (Tadao) & HIROKI (Hikokiti). Beiträge zu den Studien ueber die Persistenz der Rekurrensspirochäten im Gehirn der Mäuse. [**Studies on the Persistence of Relapsing Fever Spirochaetes in the Brain of the Mouse.**]—*Ztschr. f. Immunitätsf. u. Experim. Therap.* 1934. Mar. 15. Vol. 82. No. 1/2. pp. 1–16. With 5 figs. [12 refs.]

Studies with four freshly isolated strains of Manchurian relapsing fever and one old strain, which confirm and extend the results previously recorded by Hiroki [*ante*, p. 88].

In spite of various attempts to modify the pathogenicity of these strains by various passages, in no case was any residual brain infection produced in mice, although the freshly isolated strains were sufficiently pathogenic for human beings but only very slightly so for mice.

The authors discuss in detail the interpretation of their own experiments and the results of other workers on this subject with special reference to PRIGGE and ROTHERMUNDT's hypothesis as to the mechanism of these residual brain infections. *E. H.*

SINGER (Ernst) & FISCHL (Viktor). Der Nachweis von Arsenikalien in Spirochäten und Trypanosomen. [**The Demonstration of Arsenic in Spirochaetes and Trypanosomes.**]—*Ztschr. f. Hyg. u. Infektionskr.* 1934. Mar. 20. Vol. 116. No. 1. pp. 36–40.

FISCHL (Viktor), KOTRBA (Jan) & SINGER (Ernst). Der Nachweis von Gold in Spirochäten und Trypanosomen. [**The Demonstration of Gold in Spirochaetes and Trypanosomes.**]—*Ibid.* pp. 69–71.

Details are given for the chemical analysis of the mineral content of trypanosomes and spirochaetes in order to determine the amount of arsenic or gold in these organisms after treatment with organic arsenical compounds or gold preparations. The arsenic is estimated by a modification of the Marsh test and the gold is estimated by a spectrographic method. Both in the case of trypanosome and spirochaetal infections the results of analyses at different intervals after treatment suggest that the chemotherapeutic agents unite directly with these organisms as indicated by the metal content.

The results of analyses for arsenic in trypanosomes and spirochaetes from infected mice treated respectively with atoxyl, tryparsamide and neosalvarsan are shown in the following table :—

Nagana : 1/200 gm. Atoyxl per 20 gm. Mouse

Interval after Treatment when Blood was Collected	Volume of Blood in ccs.	Arsenic Content in γ		
		Plasma	Red Cells	Trypanosomes
10 mins.	1·1	40	0·5	0·1
25 ,, ...	1·0	48	4·0	1·0
60 ,, ...	0·7	8	5·0	0·7

Nagana : 1/100 gm. Tryparsamide per 20 gm. Mouse

Interval after Treatment when Blood was Collected	Volume of Blood in ccs.	Arsenic Content in γ		
		Plasma	Red Cells	Trypanosomes
10 mins.	1·0	30	1·0	0·3
20 ,, ...	1·2	28	0·3	0·2
30 ,, ...	0·9	50	3·0	0·3
60 ,, ...	0·7	16	0·8	0·6
180 ,, ...	1·2	3	2·5	2·5
240 ,, ...	0·7	6	2·0	1·5
Nagana : 1/600 gm. Neosalvarsan per 20 gm. Mouse				
10 mins.	0·9	2	1·6	0·0
20 ,, ...	0·7	4	0·0	0·3
Relapsing Fever : 1/600 gm. Neosalvarsan per 20 gm. Mouse.				
				Spirochaetes
10 mins.	0·9	2	2·0	0·2
25 ,, ...	0·7	16	0·0	1·0
60 ,, ...	0·3	8	1·2	0·4
120 ,, ...	1·4	7	1·0	0·8
180 ,, ...	1·5	12	0·5	1·2
300 ,, ...	0·8	6	0·2	2·2

E. H.

FELDT (Adolf). Ueber den Metallgehalt von Rekurrensspirochäten nach Behandlung infizierter Ratten mit Solganal und Salvarsan. Beitrag zum Problem der Wirkungsweise chemotherapeutischer Mittel. [**The Metal Content of Relapsing Fever Spirochaetes after the Treatment of Infected Rats with Solganal and Salvarsan. Method of Action of Chemotherapeutic Agents.**]—*Zent. f. Bakt.* I. Abt. Orig. 1934. Apr. 5. Vol. 131. No. 3/4. pp. 137–146. With 1 fig. [16 refs.]

An interesting study on the mode of action of chemotherapeutic substances in rats infected with three strains of relapsing fever spirochaetes, one normal, another resistant against salvarsan, and the other against solganal.

The infected rats were treated either with salvarsan or solganal, and 1½ to 2 hours later their blood collected, coagulation being prevented by heparin and citrate. The blood was then centrifuged for 10 minutes to remove the red cells, and then the plasma centrifuged at high speed for 2 hours to bring down the spirochaetes. The red cells and spirochaetes were washed free from the plasma and quantitative chemical analyses made of the amounts of arsenic or gold in the dried spirochaetes, red cells and plasma, respectively.

It was found that the resistant strains contained similar quantities of arsenic or gold to the normal strains, never less, a result which supports the view that salvarsan and solganal are not parasitotropic and do not act directly on the spirochaetes.

The amount of arsenic or gold found in the spirochaetes was of the same general order as that found in the dried plasma, but the red cells contained at most one-tenth this concentration. For example, in one experiment the amount of arsenic in the normal spirochaetes was 0·31, in the arsenic resistant spirochaetes 0·26, in the plasma 0·44 and 0·55, whilst the red cells contained only 0·028 and 0·029, respectively, the figures in every case indicating the number of parts per 1,000.

The action of these medicaments is considered to be through the natural defence mechanism of the animal body, and the resistance of spirochaetes to these arsenic and gold preparations to be dependent on their resistance to this defence function. Finally, the author states that the results of chemotherapeutic studies on trypanosome infections in rats and mice, are not capable of general application to other diseases, and especially not to spirochaetal infections. *E. H.*

HINDLE (E.) & WHITE (P. Bruce). **A Soluble Specific Substance in Spirochaetes.**—*Proc. Roy. Soc.* Ser. B. 1934. Mar. 2. Vol. 114. No. B790. pp. 523–529. [Summary appears also in *Bulletin of Hygiene.*]

Working with an easily cultivated strain of a water leptospira, *S. biflexa,* Wolbach and Binger, the authors immunized rabbits by inoculation at 5-day intervals with a rich suspension of cultures grown on a rabbit serum medium. With the anti-sera so produced fractions of the spirochaetal substance were tested, and one of them found to be highly specific. It was prepared by preliminary solution of the spirochaetes in 0·5 per cent. NaOH, extraction with industrial spirit, treatment of the filtrate with acetic acid, refiltration and treatment of the acid-alcohol filtrate with acetone. Then by a process of differential precipitation the acetone-insoluble fraction thus obtained was freed from protein and the result was a white, very soluble powder which gave no biuret reaction and is considered by the authors to be "either a carbohydrate, or at least a carbohydrate-containing substance." It reacted with anti-serum obtained as above in dilutions up to 1 in 100,000 but not with normal rabbit serum, which, on the other hand, contains agglutinins for the whole organism. The specific substance failed to react with anti-sera for six other water strains of spirochaetes or with anti-sera for pathogenic strains of *S. ictero-haemorrhagiae.* Since repeated injections of the substance into normal rabbits failed to produce any precipitating antibodies, it is considered to fall into the category of haptenes. *L. W. Harrison.*

HINDLE (Edward). **The Viability of Spirochaetes dried** *in Vacuo.* [Correspondence.]—*Nature.* 1934. Mar. 10. Vol. 133. No. 3358. pp. 381–382.

The author finds that it is possible to dry spirochaetes without destroying their vitality if the organisms are previously cooled to −10°C., and then dried *in vacuo* whilst in the frozen state.

Five strains of spirochaetes were tested: two culture strains of *Spirochaeta pallida,* and three strains of water leptospira. All these were found to have retained their vitality after 15 days drying *in vacuo,* and there seems no reason to doubt that they will remain alive for

much longer periods. This method, therefore, should be of value for the maintenance of strains of spirochaetes in the laboratory as it reduces the necessity for repeated subculturing. *E. H.*

JAHNEL (F.). Untersuchungen ueber das Verhalten der Pathogenität von Spirochäten auf künstlichen Nährboden, insbesondere ueber die willkürliche Beeinflussung der Pathogenität von Hühnerspirochätenkulturen. [**Studies on the Pathogenicity of Spirochaetes in Artificial Media, and Especially on Arbitrary Changes in the Pathogenicity of Cultures of Fowl Spirochaetes.**]—*Zent. f. Bakt.* I. Abt. Orig. 1933. Dec. 29. Vol. 130. No. 5/6. pp. 349–357. With 1 fig. [19 refs.]

Fowl spirochaetes grown in dilute rabbit serum containing a little coagulated egg white, were found to retain their virulence for numerous passages, but in order to infect fowls it was necessary to use young cultures.

After 43 subcultures the 4-day old cultures were found to be highly pathogenic to fowls, whilst the 8, 12, 14 and 16-day old cultures were all non-pathogenic. In these older cultures although pathogenicity has been lost, the spirochaetes retain their form and motility and can continue to live in culture media. The virulence of these spirochaetes can be restored either by making a succession of cultures at short intervals —4 days or less—or by making passages in fowls. A fowl inoculated with a non-pathogenic culture showed no signs of infection, but cultures of its blood were positive. A second fowl inoculated from the first also showed no signs of infection but blood cultures were positive, but a third fowl inoculated from the second showed a typical infection. The pathogenicity of the cultures falls lower and lower according to the number of passages, and in order to recover the pathogenicity it is necessary to make subcultures at shorter intervals. Eventually the pathogenicity is lost entirely and cannot be restored, but the ordinary growth and motility of the spirochaetes seems to be unaffected.

The inoculation of these non-pathogenic cultures into fowls, immunizes the birds against subsequent injections of virulent spirochaetes. The pathogenicity of cultures falls more rapidly at higher temperatures (37°, 40°C.) than at 33°C., and by keeping them in the ice chest loss in virulence is considerably delayed. Cultures grown at 33°C. for 3 days and then placed in the ice chest for two weeks were still virulent.

E. H.

SICARD (Marcel). Sixième cas tunisien de fièvre récurrente hispano africaine. [**A Sixth Case of Spanish African Relapsing Fever in Tunis.**] —*Arch. Inst. Pasteur de Tunis.* 1934. Mar. Vol. 23. No. 1. p. 48.

The record of another case of this disease in North Tunis. *E. H.*

GONTIER & POPOFF. Un cas de fièvre récurrente observé à Saint-Louis. [**A Case of Relapsing Fever observed in St. Louis.**]—*Bull. Soc. Path. Exot.* 1933. Dec. 13. Vol. 26. No. 10. pp. 1292–1293.

The record of an isolated case of relapsing fever observed in a native of Sor, St. Louis. *E. H.*

MÜHLENS (P.). **The Spirochaetoses.**—*Chinese Med. Jl.* 1933. Nov.–Dec. Vol. 47. Nos. 11 & 12. pp. 1384–1400.

A general account of the subject containing nothing original. *E. H.*

SAURA FARGAS (Juan). Estudios sobre la quimioterapia y el mecanismo de la inmunidad en la fiebre recurrente española.—*Medicina Países Cálidos.* Madrid. 1934. Jan. Vol. 7. No. 1. pp. 1–11. [33 refs.] French summary (9 lines).

LEPTOSPIROSIS.

GOEZ (Yann). Diagnostic de la spirochétose ictérohémorragique en Afrique Occidentale Française. [**Diagnosis of Spirochaetosis Icterohaemorrhagica in French West Africa.**]—*Thèse de Paris.* 1933. No. 546. 92 pp. [71 refs.] [Summary appears also in *Bulletin of Hygiene.*]

The author carried out the agglutination test for spirochaetosis icterohaemorrhagica in 100 serums taken from natives of French West Africa. The specimens came from individuals who had or might have had an attack of jaundice which had been regarded as yellow fever.

In 17 cases the serum agglutinated *L. icterohaemorrhagiae* in titres ranging from 1 in 5,000 to 1 in 100 and did not agglutinate allied strains of spirochaetes. In only 3 cases was coagglutination found with the Tokio strain and the *Autumnalis* A strain. In all but one case it was impossible to find the presence of lysins for *L. icterohaemorrhagiae.* The absence of these lysins does not prove that the organism is different from *L. icterohaemorrhagiae* or one peculiar to Africa, as the author's experiments on serum taken from old cases of spirochaetal jaundice showed an absence of lysins. Goez concludes that spirochaetosis icterohaemorrhagica does not exist in French West Africa and that there is no reason for supposing that the clinical forms are different from those met with on the continent of Europe. The diagnosis from other fevers associated with jaundice merely requires the agglutination test. *J. D. Rolleston.*

APPELMAN (Johan Maurits). Het isoleeren van *L. icterohaemorrhagiae* uit water. Bijdrage tot de kennis van de epidemiologie van de ziekte van Weil. [**Isolation of L.** *icterohaemorrhagiae* **from Water. A Contribution to the Epidemiology of Weil's Disease.**] [Thesis for Doctorate of Medicine at Leiden University.]—116 pp. [4 pages of refs.] 1934. Leiden: N. V. Leidsche Drukkerij-Morschsingel 14–15.

This treatise gives a very clear account of the laboratory work which has been done on infectious jaundice, or Weil's disease.

A controversy, similar in many respects to the case of cholera, centres round the question whether the water spirochaete, *L. pseudo-icterogenes* is or is not identical with the pathogenic *L. icterohaemorrhagiae,* and the author pronounces in favour of their being different organisms. Much of his work is occupied with the technical methods of testing for the presence of *L. icterohaemorrhagiae.* The mouse is quite a suitable animal to use for this purpose and the organisms may be found in the peritoneal fluid after intraperitoneal

injection. Not only so—and this is important diagnostically, especially for an avirulent strain—the serum may show the evidence of infection by an agglutination-lysis test even if the peritoneal fluid fails to do so. One of the chief contributions of the author to original work on his subject is his "bath" test for the isolation of *L. icterohaemorrhagiae* from water and its separation from *L. pseudoicterogenes*. A guineapig is the animal used. After shaving and scarifying the abdomen the animal is placed in a glass dish and about 3 litres of test water, warmed to 30°C., filled into the dish until it reaches to the flanks of the animal. In this it continues sitting for an hour, after which it is placed, without drying, in a warm cage for 5 hours. Artificially infected water was used in the experiments and the minimum degree of infection which was successful amounted to one leptospira per 3 cc. water. Success was also obtained with ditch water. The disease ran an especially acute course when infection took place with natural water. After an incubation period of 6 to 10 days according to the number of leptospirae present, the temperature rises to above 40°C. On the second day the fever sinks. Severe jaundice sets in on the third day and then on that day or the next death supervenes. The *Leptospira pseudoicterogenes*, which may be present in abundance in the water under test is not at all pathogenic and consequently the organism isolated from the organs of the animal dead of Weil's disease is pure *L. icterohaemorrhagiae*. It would seem therefore that the author has surmounted the difficulty of proving the presence of *L. icterohaemorrhagiae* in water, even if it contain *L. pseudoicterogenes* and be highly contaminated with faecal organisms. *W. F. Harvey.*

Troisier (J.), Bariéty (M.), Erber (B.) & Gabriel (P.). Existe-t-il une spirochétose occulte d'origine hydrique ? [**Is there an Occult Spirochaetosis of Water Origin ?**]—*Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 1934. Jan. 22. 50th Year. 3rd Ser. No. 1. pp. 26–29.

The authors tested the serum of a patient convalescent from a phlegmonous angina, and found that it agglutinated the Verdun strain of *Spirochaeta icterohaemorrhagiae* up to dilutions of 1/100. This patient had never shown any signs of spirochaetal jaundice, but was devoted to aquatic sports and it is suggested that he might have acquired a purely latent infection from the water. *E. H.*

Moriguchi (Takeji). **The Effect of Bismuth upon Experimental Akiyami.**—*Japanese Jl. Experim. Med.* 1933. Aug. 20. Vol. 11. No. 4. pp. 353–356. [31 refs.]

Akiyami is a spirochaetal disease resembling but not identical with Weil's disease. The authors have found that 1 per cent. solutions of "tartaro-bismuth potassium sodium" have a positive effect when injected into guineapigs 48 hours after inoculation of the spirochaetes.

D. H.

Roskott (E. R. A. Luyke). De ziekte van Weil op Billiton.—*Geneesk. Tijdschr. v. Nederl.-Indië.* 1934. Jan. 30. Vol. 74. No. 3. pp. 178–181.

RAT-BITE FEVER.

VASSILIADIS (P.). Découverte du *Spirillum minus* en Egypte. **[The Discovery of *Spirillum minus* in Egypt.]**—*C. R. Soc. Biol.* 1934. Vol. 115. No. 4. pp. 444–446.

The author found specimens of *S. minus* in the blood of a splenectomized rat (*Mus norvegicus*) captured at Suez. The blood was negative 3 days after the operation and positive on the 6th day. A guinea-pig inoculated subcutaneously with the blood of this rat failed to become infected. *E. H.*

ARIMA (Shizuka). **Experimental Inquiry into the Transmission of Rat-Bite Fever among Rats : Part I.**—*Philippine Jl. Sci.* 1933. Oct. Vol. 52. No. 2. pp. 89–95.

Fleas [species not stated] were fed on rats infected with the Manila strain of *Spirillum minus* and subsequently tested for infectivity. The spirilla remained alive for one hour after ingestion and also retained their infectivity, as tested by inoculation into guineapigs, but after longer intervals failed to produce any infection. Attempts to transmit the disease by the bites of infected fleas gave uniformly negative results. *E. H.*

BLACHER (W.). Ueber Spirozidbehandlung der Rattenbisskrankheit (Sodoku). **[The Spirocid Treatment for Rat-Bite Fever (Sodoku).]** —*Muench. Med. Woch.* 1934. Apr. 20. Vol. 81. No. 16. pp. 591–592. With 1 chart.

The description of a case of sodoku in a 2 year-old-boy, who was given varying doses of spirocid. Small doses ($\frac{1}{4}$ tablet) seemed to provoke a febrile reaction, but the treatment was continued and the dose gradually increased to 2 tablets. After 2 months the patient was cured without any secondary toxic symptoms having developed although 9 gm. of the drug had been given. *E. H.*

REVIEWS AND NOTICES.

CHRISTOPHERS (S. R.), SINTON (J. A.) & COVELL (G.). **How to do a Malaria Survey.**—*Health Bull. No. 14. Malaria Bureau No. 6.* Calcutta. 2nd Edition. 1931. pp. iv+174. With 11 plates & 3 figs. [As.10 or 1s.]

This book was originally issued in 1928 as a guide for students of malaria in India, and more especially to aid those attending the malaria course of the Malaria Survey of India. It is an indispensable guide for those engaged on malaria surveys, and it is not surprising that the first edition was exhausted within a year. The new edition contains many valuable additions such as methods for making permanent preparations of larvae, and of the infected gut of mosquitoes. There is also a table for differentiating between the parasites of human and avian malaria, and a note on the use of the precipitin test as a means of determining the source of anopheline blood meals. Other additions are Sinton's method of estimating the amount of quinine in medicinal solutions, by the use of Tanret's reagent and Brown's barium sulphate opacity tubes, a field method for estimating the salinity of water, and a note on the construction and use of Barraud's cages for the transport of mosquitoes. A list of the Indian anopheles is given which shows their distribution, breeding places, and importance with regard to malaria. *A. culicifacies, A. listonii, A. ludlowii, A. maculatus, A. minimus,* and *A. stephensi* are starred as the most important carriers. An index is another useful addition.

Some alterations have been made in those sections of the book which deal with the enlarged spleen, and with the " terms and conceptions " used in malaria work ; the invaluable chapter on the dissection of mosquitoes remains unaltered. Two sections, the one dealing with the equipment of the field laboratory and the other with the preparation of maps, have been moved from the middle of the book to the appendix. This has caused some confusion in the cross references ; for instance, on p. 13, section X should read section VIII, on pp. 38 and 40, VII should be VI, and on p. 66, sub-section (*d*) should be appendix XIII.

The new edition ends with the same wise words as the old one : " It is easy enough to recommend the oiling, etc., of all breeding places in an area, but not so easy to arrange that this will be correctly carried out during the year. It is in regard to the last part of the arrangement that the plans of the malaria officers are usually lacking in definiteness."

W. Fletcher.

BARRAUD (P. J.) [F.E.S., F.Z.S., F.L.S., etc.]. **The Fauna of British India, including Ceylon and Burma. Diptera. Vol. 5. Family Culicidae. Tribes Megarhinini and Culicini.**—pp. xxviii + 463. With 106 figs., 8 plates and 1 folding map. Published under the Authority of the Secretary of State for India in Council. Edited by Lt.-Col. R. B. S. SEWELL, C.I.E., Sc.D., I.M.S., assisted by F. W. EDWARDS, M.A., Sc.D. 1934. Mar. London : Taylor & Francis, Red Lion Court, Fleet Street.

CHRISTOPHERS' account of the Indian Anophelines* has been followed at a very short interval by the present volume, which deals

* The reviewer was in error in stating (this *Bulletin*, Vol. 31, p. 74) that *Anopheles stephensi* " ranges eastwards through the Malay States and the East Indies."

with the rest of the mosquitoes (Megarhinini and Culicini), also with the related Dixinae and Chaoborinae which are not of medical importance.

In the present volume, Captain Barraud discusses about 300 species of which approximately 250 are Culicini. It follows that a large part of the work is purely systematic, and that general and introductory matter has been reduced to a minimum ; but the introductory chapters to the volume by CHRISTOPHERS apply for the most part to the insects which are here considered. In spite of Captain Barraud's investigations on Indian Culicine mosquitoes, which have continued for about a dozen years, there seems little doubt that many species still remain unknown—indeed, the present book contains an appendix describing half a dozen which were discovered while the work was passing through the press. But it is certain that the present volume will remain a standard authority for many years to come, and workers in India, and indeed throughout the Oriental region, must be extremely glad of its publication.

The systematic entomologist will note with pleasure that the larvae of most of the Indian Culicines are known though 96 remain to be described. One observes also short descriptions of some of the pupae and eggs. The excellent photographs which appear on plates at the end will render the identification of many species, particularly of the subgenera *Finlaya* and *Stegomyia*, an easy matter. Those who have used Barraud's long series of systematic papers are already familiar with his excellent photographic work.

To the medical reader the volume is of rather limited interest, though it has considerable potential value in relation to yellow fever, dengue and filariasis : also because of the irritation caused by domestic mosquitoes. One might be glad of more detailed information about the distribution of *Stegomyia aegypti* in the Indian Empire : we are told that it is widely distributed and the map of its distribution bears this out, but is it found only in ports and large towns (perhaps by way of railway lines) or is it found also in remote villages throughout the country ?

The volume, which is very well illustrated by text-figures, concludes with a folding map of the Indian Empire and Ceylon.

P. A. Buxton.

FISCHL (Viktor) & SCHLOSSBERGER (Hans). **Handbuch der Chemotherapie. Zweiter Teil. Metallderivate.** [Handbook of Chemotherapy, Part II. Metallic Derivatives.]—pp. xi+359–898. 1934. Leipzig : Fischers medizinische Buchhandlung. [M.55.]

The first volume of this compendious handbook of Chemotherapy, which deals with non-metallic organic derivatives, was reviewed in this *Bulletin*, 1932, Vol. 29, p. 733. The second volume contains an account of those chemotherapeutic substances which owe their activity to the presence of a non-metallic radical. The most important sections naturally deal with arsenic and antimony, but full consideration is also given to bismuth, iodine, copper, gold and mercury. The chemotherapeutic action of some 48 other elements is also mentioned.

The use of each element is first of all considered from an historical aspect. Arsenic in the form of a sulphide was originally used by Hippocrates as an application to boils : the virtues of iodine were early appreciated by the Chinese, perhaps the result of a racial tendency to

slight thyroid deficiency which, if Keith's view be correct, is responsible for many of their physical characteristics. Gold was much esteemed in India centuries before the Christian era. The history of each metal is followed by a consideration of the chemotherapeutic use of the free metal and of its various compounds inorganic and organic. Pharmacology, chemical constitution, mode of action and toxicity for animals are fully dealt with, while appended to each chapter is a very complete bibliography. Even in the case of an element such as gold the bibliography comprises between eight and nine hundred references. As all these references are also mentioned in the text it follows that at times reading is no light matter, especially when compact lists of from forty to sixty names are encountered. From what has already been said it is obvious that the book is of an encyclopaedic character and, as a work of reference, it will prove invaluable. If perhaps any sections lack exhaustive treatment it is those which deal with the pathological lesions produced by chemotherapeutic agents. Thus, in considering the toxic action of the arsphenamines, no reference is given to the Medical Research Council's two special Reports: Phelps's analysis of the effects of nearly 200,000 doses of neoarsphenamine administered in the U.S. Navy also passes unnoticed. The use of the symbol Ø will not be familiar to all, while in none of the seventeen tables where it occurs is its exact significance explained.

The book closes with an index of all the chemical compounds mentioned in this and the preceding volume. *G. M. Findlay.*

Wu Lien-Teh, Chun (J. W. H.), Pollitzer (R.) & Wu (C. Y.). **Cholera. A Manual for the Medical Profession in China.**—pp. xxii + 197. With 1 colour & 23 half-tone plates. 1934. Shanghai, China: National Quarantine Service, 2 Peking Road. [Cloth 12s.; paper 10s. 6d.]

This manual is the first of a series on the commoner epidemic diseases of China and should provide a sound guide on technique, treatment and prevention. Each author deals with a special section. The first of these is an interesting historical and epidemiological discussion by Dr. Wu Lien-Teh, Director of the National Quarantine Service. In the oldest work on Chinese medicine, about 2,600 B.C., there is mention of a disturbance of the alimentary tract which is given two script characters, "Huo luan." The term represented a syndrome of cholera and cholera-like affections. It was not however "until the latter half of the Ch'ing (Manchu) Dynasty (1644–1911) that symptoms relating to cholera were mentioned in detail." An important chapter on the laboratory aspects of cholera follows in which, besides the morphology, the biology of the vibrio receives adequate presentation. A very satisfactory feature of this chapter is the cautious way in which the author deals with the controversial subjects of immunization in cholera, transmutation of vibrios and the rôle of cholera carriers. This manual is not intended for the laboratory worker only. It also deals with the clinical aspects of the disease, including treatment, in part three. In a country like China and with a disease like cholera where the people themselves must be persuaded to co-operate with public authorities, if the disease is to be prevented from assuming epidemic proportions, education and propaganda will naturally require special attention. This subject receives treatment in part four. "A vast, little developed field lies

before the educational and publicity health worker in China. He is confronted at the very outset with the problem of four hundred million human beings steeped in millennium-old customs and superstitions." Many methods of publicity are considered. Sky writing by aeroplane, however, is evidently not considered worth attempting owing to the complicated architecture of the Chinese language. An appendix on the spread and control of sea-borne cholera concludes this praiseworthy and serious attempt to provide detailed instruction for the medical profession in China on one of the most terrifying, fatal and at the same time most preventable diseases of mankind.

W. F. Harvey.

PINEY (A.) [M.D., M.R.C.P., etc.]. **Blood Diseases in General Practice.** —92 pp. Pocket-Monographs on Practical Medicine. 1934. London: John Bale, Sons & Danielsson, Ltd. [2/6]

It is much more difficult to write a small book on a large subject than a large book on a small subject. There is already a number, almost a library, of works on Haematology and this additional "pocket-monograph" does not occupy much space, but whether it will "fill the gap in our literature," as the author hopes, is not for us to prophesy. He disarms criticism by stating in a short preface that he is well aware of the incompleteness of the book.

The work is difficult to place. If it is "to stimulate interest in blood diseases," it might be expected to rate as an elementary introduction, but it is not this since it is "taken for granted that the reader has some knowledge of the various types of blood-cells." It is obviously impossible to convey much information on the blood, the anaemias, leukaemias, haemorrhagic diatheses, lymphadenoma, splenic diseases, infectious mononucleosis and agranulocytosis, together with the treatment of them in 90 small pages. Industrial poisons too are not omitted. Agranulocytosis is probably the most important of blood conditions of recent times in which the practitioner needs information, but the treatment suggested is too indefinite to be of much assistance: stimulation of the marrow by "exposure of the long and flat bones to very small doses of X-rays" and the use of pentnucleotide "which should be injected intramuscularly every day" till reaction is obtained, are the chief but no indications are given as to dosage. There are some useful hints on the administration of iron.

The blood changes, anaemias and infections leading to them, such as are commonly met with by those practising in tropical countries are not touched upon.

H. H. S.

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